National Clinical Guideline Centre

Draft for consultation, December 2014

Type 1 diabetes

Type 1 diabetes: diagnosis and management of type 1 diabetes in adults

Clinical guideline <...>

Appendices H-U

December 2014

Draft for consultation

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None

H.2 Education programmes and self-care

Table 1: KRUGER2013

J. Kruger, A. Brennan, P. Thokala, H. Basarir, R. Jacques, J. Elliott, S. Heller, and J. Speight. The cost-effectiveness of the Dose Adjustment for Normal Eating (DAFNE) structured education programme: An update using the Sheffield Type 1 Diabetes Policy Model. Diabetic Medicine 30 (10):1236-1244, 2013.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY) **Study design:** Deterministic decision analytic model based on the Sheffield Type 1 Diabetes Policy Model. **Approach to analysis:** HbA1c was the key surrogate outcome influencing long-term diabetes-related complications modelled through the Sheffield Type	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 40 M =45% **Intervention 1:** Current standard practice **Intervention 2:** 5-day structured education programme (DAFNE) delivered according to a structured curriculum in groups of six to	**Total costs (mean per patient):** Intervention 1: £72,426 Intervention 2: £72,852 Incremental (2-1): £426 (CI NR; p = NR) **Currency & cost year:** 2011/2012 GBP **Cost components incorporated:** DAFNE intervention, insulin, long-term complications, adverse events	**QALYs (mean per patient):** Intervention 1:9.7429 Intervention 2:9.7723 Incremental (2-1): 0.0294 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £14,475 per QALY gained (95% CI: £10,110 – 18,690) Probability Intervention 2 cost-effective (£20K threshold): 54% **Analysis of uncertainty:** a) 6-month HbA1c predicted from RCT as 12-month: DAFNE is dominant b) 4-year HbA1c maintained to 7 years: ICER £13,791 per QALY gained c) 4-year HbA1c maintained for lifetime: DAFNE dominant d) 6-month HbA1c predicted from RCT as 12-month and 4-year HbA1c maintained to 7 years: DAFNE dominant

1 Diabetes Policy Model. **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:** 5 years in base case **Discounting:** Costs = 3.5%; Outcomes = 3.5%	eight participants, teaching skills in flexible intensive insulin therapy with a focus on adjusting insulin doses to match carbohydrate intake, increasing dietary freedom.			e) 12 month HbA1c maintained to year 7: DAFNE dominant f) 6-month HbA1c predicted from RCT as 12-month and maintained to year 7: DAFNE dominant g) HbA1c returns to baseline levels after 1 year: ICER £78,227 per QALY gained h) 6-month HbA1c predicted from RCT as 12-month and HbA1c returns to baseline levels after 1 year: ICER £7,418 per QALY gained i) Probabilities of severe hypoglycaemia and ketoacidosis differ between arms and linked to HbA1c based on research database: DAFNE dominant
Data sources				
Health outcomes: patient-level data sets; HbA1c change after DAFNE was based on analysis of the longer-term follow-up data from the DAFNE RCT. Assumption: HbA1c returns to baseline levels at year 5; in the control arm HbA1c level is unchanged from baseline; risk of severe hypoglycaemia was the same in both arms; no reduction in the incidence of ketoacidosis following DAFNE. **Quality-of-life weights:** Sheffield Type 1 Diabetes Policy Model. **Cost sources:** Sheffield Type 1 Diabetes Policy Model.				
Comments				
Source of funding: National Institute for Health Research (NIHR) **Limitations:** Sheffield Type 1 Diabetes Policy Model used published data from non-UK settings to define risk of long-term complications, some of which are now very old (e.g. DCCT). Old and non-UK data may not accurately represent the incidence of complications in the UK DAFNE population. It is possible not all the costs were included as PSS costs were not included. The analysis used only HbA1c change to represent the clinical effectiveness of DAFNE. The analysis relies on extrapolation and assumptions on HbA1c levels.				
Overall applicability*: Directly applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER, incremental cost-effectiveness ratio; NR, not reported; STTP, structured teaching and treatment programme; QALYs, quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.3 Blood glucose monitoring

Table 2: HUANG2010

Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2010; 33(6):1269-1274. (Guideline Ref ID HUANG2010)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Discrete simulation model **Approach to analysis:** Simulation model that allows for the simultaneous progression of diabetes through major complications including retinopathy, nephropathy, neuropathy, ischemic heart disease, myocardial infarction, congestive heart failure and stroke. All these modules have Markov sub-models underneath them. Perspective: US health care system	**Population:** This analysis compared two cohorts: HbA1c ≥7.0% in adults and HbA1c ≤7.0% in all age groups. Only the results for the applicable population are presented here. Population characteristics: Start age = 43 M = 44% n=98 duration of diabetes = 22.75 years Intervention 1: Self-monitoring of blood glucose Intervention 2: Real-time continuous glucose monitoring with self-monitoring of blood glucose	Total costs (mean per patient): Intervention 1: £105,237 Intervention 2: £143,533 Incremental (2-1): £38,297 (CI NR; p = NR) Currency & cost year: 2010 US dollars (presented here as 2010 UK pounds‡) Cost components incorporated: Direct costs including cost of CGM, insulin, finger sticks, office visits, emergency room visits, hospitalisations, out-of-hours visits and costs associated with complications. Indirect costs including time devoted to diabetes by the patient, caregiver and secondary caregiver; days off work to the patient, caregiver	QALYs (mean per patient): Intervention 1: 13.75 Intervention 2: 14.35 Incremental (2-1): 0.60 (CI NR; p = NR)	ICER (Intervention 2 vs. Intervention 1): £63,828 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Analysis of uncertainty: The authors undertook univariate sensitivity analysis to assess the effect on the societal ICER. Parameters analysed were; removal of immediate quality-of-life gain, number of test strips used with CGM and the daily CGM cost. When the benefit of CGM is limited to glucose lowering and subsequent complication prevention, QALY gained reduces to 0.08 and the societal ICER increases to £474,787 per QALY. However, if the number of test strips used were to fall to the recommended two strips per day for calibration, CGM would be cost-saving. There is considerable uncertainty around the ICER, as shown by the confidence interval around the base case societal ICER, running from dominant to dominated.

Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2010; 33(6):1269-1274. (Guideline Ref ID HUANG2010)				
Time horizon: Lifetime Treatment effect duration: Lifetime Discounting: Costs = 3% ; Outcomes = 3%		and secondary caregiver.		
Data sources				
Health outcomes: Baseline event data taken from previous economic evaluations and large diabetes trials. Effectiveness data derived from a single randomised trial.[488,489] Quality-of-life weights: Health Utility Index and time trade-off utilities. Cost sources: Red Book, American Diabetes Association, Medicare fee schedule, trial cost diaries, previous economic evaluations				
Comments				
Source of funding: Study funding was provided by the JDRF, which receives significant funding from the pharmaceutical and medical devices industry. Certain authors have received funding for their respective departments from these companies; however, none had any involvement in the design, conduct, and analysis of the trial or of the cost-effectiveness analysis. Limitations: Although the model included many health states, it does not include hypoglycaemia. One of the main benefits of CGM is the reduction in hypoglycaemic events and the fear of hypoglycaemia. Including this outcome may have increased the benefits of the CGM arm and reduced the costs compared to SMBG, providing a more favourable ICER. The effectiveness data was derived from a single trial and there is no indication that a systematic review was undertaken to identify all relevant evidence. Discount rates and utilities are not in line with NICE reference case. The sensitivity analysis was limited. Other: This analysis also presented a within trial analysis, however this has not been reported here as it was not as applicable as the lifetime model analysis. The study only presented the ICER for the societal perspective. The ICER for the direct cost analysis has been calculated by the NCGC. Cost year not provided so assumed same as publication year.				
Overall applicability*: Partially applicable **Overall quality**: Potentially serious limitations**				

Abbreviations: CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CGM, continuous glucose monitoring; CI, 95% confidence interval; CUA, cost-utility analysis; da, deterministic analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; NCGC, National Clinical Guideline Centre; NICE, National Institute for Health and Care Excellence; NR, not reported; pa, probabilistic analysis; SMBG, self-monitoring of blood glucose; QALYs, quality-adjusted life years

‡ Converted using 2007 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 3: MCQUEEN2011

McQueen RB, Ellis SL, Campbell JD, Nair K, V, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Effectiveness and Resource Allocation. 2011; 9:13:13. (Guideline Ref ID MCQUEEN2011)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model of progression of 12 different diabetes disease states, using a cycle length of 1 year, allowing for up to four concurrent comorbidities. At the start, the population can move from no complication to one of six states; retinopathy, nephropathy, neuropathy, CHD, no complications or death. From the five complications, the population can enter an additional seven disease states; nephropathy and CHD,	**Population:** Adults with type 1 diabetes with a mean HbA1c level greater than 7.0% **Cohort settings:** Start age = 40 M = 58.6† n=NR duration of diabetes = 20 years **Intervention 1:** Self-monitoring of blood glucose **Intervention 2:** Real-time continuous glucose monitoring with self-monitoring of blood glucose	**Total costs (mean per patient):** Intervention 1: £303,546 Intervention 2: £318,739 Incremental (2-1): £15,193 (CI NR; p = NR) **Currency & cost year:** 2007 US dollars (presented here as 2007 UK pounds‡) **Cost components incorporated:** 1) Cost of diabetes: Hospital inpatients, nursing or residential facility, physicians office, emergency department, ambulance services, hospital outpatients, home health, hospice, podiatry, insulin, diabetic supplies, oral agents, retail prescriptions, other supplies, patient time through lost wages. 2) CGM costs 3) Marginal costs for each disease state were calculated using average length of stay	**QALYs (mean per patient):** Intervention 1: 10.289 Intervention 2: 10.812 Incremental (2-1): 0.523 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £29,029 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective ($50K/£30K threshold): 48% **Analysis of uncertainty:** Probabilistic sensitivity analysis was used to assess the uncertainty around the ICER. At a £30K per QALY threshold, CGM with SMBG has a 48% probability of being cost effective compared to SMBG alone. Considerable univariate sensitivity analysis was conducted by varying parameters by ± 15%. This identified the ten most sensitive variables which were then varied by ± 50% to estimate their possible effects on the model. Of these, the ICER was most sensitive to changes in the utility of diabetes with no complications, the annual cost of CHD and, the probability of transition from diabetes with no complications to the CHD state.

McQueen RB, Ellis SL, Campbell JD, Nair K, V, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Effectiveness and Resource Allocation. 2011; 9:13:13. (Guideline Ref ID MCQUEEN2011)				
neuropathy and CHD, retinopathy and CHD, neuropathy and nephropathy, blindness, ESRD, lower extremity amputation and neuropathy, or death. **Perspective:** US societal **Time horizon:** 33 years **Treatment effect duration:** lifetime **Discounting:** Costs = 3% ; Outcomes = 3%		and cost per medical event		
Data sources				
Health outcomes: Reductions in the risk of complications were drawn from two sources: DCCT[491] (microvascular conditions) and a meta-analysis[452,452](macrovascular conditions). Effectiveness data derived from a single randomised trial, Tamborlane2008[488,489] **Quality-of-life weights**: EQ5D US tariff[483,483]. **Cost sources**: Cost of diabetes and marginal cost of disease states derived from evidence published by the American Diabetes Association. Cost of CGM obtained from a diabetes technology website.				
Comments				
Source of funding: NR. **Limitations**: This analysis was performed from a societal perspective. Although the model included many health states, it does not include hypoglycaemia rates. One of the main benefits of CGM is the reduction in hypoglycaemic events and the fear of hypoglycaemia. Including this outcome may have increased the benefits of the CGM arm and reduced the costs compared to SMBG, providing a more favourable ICER. The probabilities of events are drawn from many different sample populations. The CGM arm includes all the costs associated with SMBG, however, those with CGM do not need SMBG as regularly. The model also assumes that there is a constant probability of diabetes complications overtime which is unlikely to be realistic. The effectiveness data was derived from a single trial and there is no indication that a systematic review was undertaken to identify all relevant evidence. Discount rates are not in line with NICE reference case. Although				

McQueen RB, Ellis SL, Campbell JD, Nair K, V, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Effectiveness and Resource Allocation. 2011; 9:13:13. (Guideline Ref ID MCQUEEN2011)
EQ-5D is used, the US tariff is used. **Other:** This analysis also presented a within trial analysis, however this has not been reported here as was not as applicable as the lifetime model analysis.
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: CCA, cost-consequence analysis; CEA, cost-effectiveness analysis; CGM, continuous glucose monitoring; CI, 95% confidence interval; CUA, cost-utility analysis; da, deterministic analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; NCGC, National Clinical Guideline Centre; NICE, National Institute for Health and Care Excellence; NR, not reported; pa, probabilistic analysis; SMBG, self-monitoring of blood glucose; QALYs, quality-adjusted life years

†Assumed from the clinical trial

‡ Converted using 2007 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.4 Insulin therapy

Table 4: CAMERON2009

Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. Canadian Medical Association Journal. 2009; 180(4):400-407. (Guideline Ref ID CAMERON2009)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness (a)**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes	**Population:** Adults with type 1 diabetes specific to a Canadian setting. **Cohort settings:** Start age = 27 M = 53.5% Duration of diabetes = 9 years BMI (kg/m^2) = 23.75 Weight (kg) = 68.83 **Short acting:**	**Total costs (mean per patient):** **Short acting:** Intervention 1a: £38,435 Intervention 1b: £38,234 Intervention 2: £38,084 Intervention 3: £38,331 Incremental (2-1a): -£351 (CI NR; p = NR) Incremental (3-1b): £97 (CI NR; p = NR) Incremental (3-2): £248† (CI NR; p = NR)	**QALYs (mean per patient):** **Short acting:** Intervention 1a: 10.961 Intervention 1b: 10.991 Intervention 2: 11.016 Intervention 3: 10.997 Incremental (2-1a): 0.055 (CI NR; p = NR) Incremental (3-1b): 0.006 (CI NR; p = NR) Incremental (3-2): -0.019† (CI NR; p = NR)	**Short acting:** **ICER (Intervention 2 vs. Intervention 1a):** Insulin aspart is dominant over regular human insulin CI: NR Probability Intervention 2 cost-effective (≈£26K threshold): 52.3% **ICER (Intervention 3 vs. Intervention 1b):** £15,442 per QALY gained CI: NR Probability Intervention 3 cost-effective (≈£26K threshold): 46.1%

Perspective: Canadian third-party payer **Time horizon:** 50 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	**Intervention 1:** **a:** Regular human insulin (0.68 IU/kg) **b:** Regular human insulin (0.68 IU/kg) **Intervention 2:** Insulin aspart (0.52 IU/kg) **Intervention 3:** Insulin lispro (0. IU/kg) **Long acting:** **Intervention 4:** **a:** NPH (0.34 IU/kg) **b:** NPH (0.34 IU/kg) **Intervention 5:** Insulin glargine (0.28 IU/kg) **Intervention 6:** Insulin detemir (0.28 IU/kg)	**Long acting:** Intervention 4a: £35,856 Intervention 4b: £36,411 Intervention 5: £37,679 Intervention 6: £38,724 Incremental (5-4a): £1823 (CI NR; p = NR) Incremental (6-4b): £2313 (CI NR; p = NR) Incremental (6-5): £1045† (CI NR; p = NR) **Currency & cost year:** 2007 Canadian dollars (presented here as 2005 UK pounds‡) **Cost components incorporated:** Insulin regimens, inpatient and outpatient services, emergency department visits. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer,	**Long acting:** Intervention 4a: 11.097 Intervention 4b: 11.034 Intervention 5: 11.136 Intervention 6: 11.045 Incremental (5-4a): 0.039 (CI NR; p = NR) Incremental (6-4b): 0.011 (CI NR; p = NR) Incremental (6-5): 0.011† (CI NR; p = NR)	**ICER (Intervention 3 vs. Intervention 2):** Insulin lispro is dominated by insulin aspart† CI: NR Probability Intervention 3 cost-effective (≈£26K threshold): NR **Long acting:** **ICER (Intervention 5 vs. Intervention 4a):** £46,829 per QALY gained CI: NR Probability Intervention 5 cost-effective (≈£26K threshold): 25.1% **ICER (Intervention 6 vs. Intervention 4b):** £206,488 per QALY gained CI: NR Probability Intervention 6 cost-effective (≈£26K threshold): 10.8% **ICER (Intervention 6 vs. Intervention 5):** £95,000 per QALY gained † CI: NR Probability Intervention 6 cost-effective (≈£26K threshold): NR% **Analysis of uncertainty:** For each analysis 1,000 mean cost and effect pairs, each of 1,000 iterations were calculated for each treatment group. This analysis was most sensitive to changes in HbA1c and utilities scores attached to hypoglycaemia. All insulin analogues became either dominant or cost-effective over conventional insulin when a reduction in the fear of hypoglycaemia is

		amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity..		incorporated within the model.
Data sources				
Health outcomes: Baseline event data was taken from the IMS-CDM. Effectiveness data was from a well conducted meta-analysis[76,467] **Quality-of-life weights:** EQ-5D US tariff. **Cost sources:** Ontario Drug Benefits Formulary 2008, Comparative Drug Index 2006, PPS 2007				
Comments				
Source of funding: Health Canada **Limitations:** There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** This paper is the abridged version of a full CADTH report[75]; the analyses comparing insulin aspart with insulin lispro and insulin glargine with insulin detemir were calculated by the NCGC using data provided; if a full incremental analysis had been conducted and intervention 6 had been compared against 4a, insulin detemir would have been dominated by NPH.				
Overall applicability*: Partially applicable Overall quality: Minor limitations**				

Abbreviations: BMI, body mass index; CADTH, Canadian Agency for Drugs and Technologies in Health; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-Centre for Outcomes Research Diabetes Model; IU, international units; NCGC, National Clinical Guideline Centre; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; UKPDS, United Kingdom Prospective Diabetes Study

†These analyses have been calculated by the NCGC using data provided in the analyses

‡ Converted using 2007 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations / Potentially serious limitations / Very serious limitation*

Table 5: GRIMA2007

Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics. 2007; 25(3):253-266. (Guideline Ref ID GRIMA2007)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = LY and QALY)	**Population:** Adults with type 1 diabetes who do not reach the recommended target (HbA1c ≤7%) with multiple daily	**Total costs (mean per patient):** Intervention 1: £26,490 Intervention 2: £27,233	**QALYs (mean per patient):** Intervention 1:10.666 Intervention 2:10.733 Incremental (2-1): 0.067	**ICER (Intervention 2 vs. Intervention 1):** £10,903 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective

Study design: Deterministic decision analytic model **Approach to analysis:** Markov model used to model the number and risk of micro-and macrovascular complications and deaths dependant on HbA1c levels (7-8%, 8-9%, 9-10% and >10%). **Perspective:** Canadian public payer perspective **Time horizon:** 36 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	injections of NPH insulin. **Cohort settings:** Start age = 27 M = NR n=NR HbA1c = 7% - 10% BMI = NR Weight = NR Duration of diabetes (years) = NR **Intervention 1:** NPH (27.17IU daily dose) **Intervention 2:** Insulin glargine (22.16IU daily dose)	Incremental (2-1): £733 (CI NR; p = NR) **Currency & cost year:** 2005 Canadian dollars (presented here as 2005 UK pounds‡) **Cost components incorporated:** Insulin costs and complication costs. Non- fatal complications in this model included: myocardial infarction, stroke, heart failure, end-stage renal disease, retinopathy and lower extremity amputation. Fatal complications include myocardial infarction, stroke, heart failure, end-stage renal disease and lower extremity amputation. Complication costs included costs for inpatient care, home healthcare, outpatient therapy, physician visits, day care and diagnostic and therapeutic procedures.	(CI NR; p = NR)	(£20K/30K threshold): NR **Analysis of uncertainty:** Deterministic sensitivity analysis was undertaken on insulin glargine efficacy, the cost of treating diabetes, utilities and discount rates. The ICER was most sensitive to the efficacy of glargine. When varied between a HbA1c reduction of 0.14% and 0.5% the ICER varies between £89,170 and £4,904 per QALY gained.
Data sources				
Health outcomes: The baseline rates of micro- and macro vascular complications and deaths were derived from a previous economic evaluation. UKPDS data was used to estimate the proportional change in complication risk with change in HbA1c. A single study provided the effectiveness data[410,410]. Q**uality-of-life weights:** Utilities were derived from two sources; UKPDS data that used the EQ5D UK tariff and a study using the Quality of Wellbeing – Self Assessment tool. **Cost sources:** Complication costs come from two previously published economic evaluations in Canada. Insulin glargine costs were provided by Aventis Canada. NPH insulin was taken from 'Liste				

de médicaments publiée par la Regie de l'assurance maladie de Québec' 2003.
Comments
Source of funding: Sanofi-Aventis. **Limitations:** Although a systematic review was undertaken, one study was chosen from these as being an average representation; there is very limited detail provided on the cohorts' characteristics; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; insulin use is provided but no other resources are; particular complication costs were taken from previous economic evaluations; the cost for insulin glargine was provided by the manufacturer and many not be representative of the true cost; uncertainty around particular key clinical inputs were not explored in a sensitivity analysis; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%.
Overall applicability*: Partially applicable Overall quality: Very serious limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; LY, life years; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; UKPDS, UK Prospective Diabetes Survey

‡ Converted using 2005 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 6: MCEWAN2007

McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Current Medical Research and Opinion. Newbury, United Kingdom, Newbury: Informa Healthcare. 2007; 23:S7-S19. (Guideline Ref ID MCEWAN2007)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome =QALY gained) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Simulation model incorporating seven interdependent complications in either fatal or non-fatal states or in ascending	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 27 M = 54% n=1,000 HbA1c = 8.8% BMI = NR Weight (kg) = 72 Duration of diabetes (years) = NR **Intervention 1:**	**Total costs (mean per patient):** Scenario 1: Intervention 1: £9,805 Intervention 2: £8,708 Incremental (2-1): £1,097 (CI NR; p = NR) Scenario 2: Intervention 1: £9,784 Intervention 2: £8,703 Incremental (2-1): £1,080 (CI NR; p = NR)	**QALYs (mean per patient):** Scenario 1: Intervention 1: 10.97 Intervention 2: 10.84 Incremental (2-1): 0.12 (CI NR; p = NR) Scenario 2: Intervention 1: 10.97 Intervention 2: 10.84 Incremental (2-1): 0.12 (CI NR; p = NR) Scenario 3:	**ICER (Intervention 2 vs. Intervention 1):** Scenario 1: £8,807 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Scenario 2: £8,668 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Scenario 3: £7,391 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective

severity to consider five scenarios using different data and assumptions. **Perspective:** UK NHS **Time horizon:** 40 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 3.5% ; Outcomes = 3.5%	NPH **Intervention 2:** Insulin glargine A daily basal requirement of 25% of the total daily insulin requirement was assumed for both regimens, yet doses were not provided **Scenarios:** Scenario 1: 25% risk reduction in severe hypoglycaemic events; a 19% rate reduction in nocturnal hypoglycaemia; no improvement in HbA1c Scenario 2: 26% risk reduction in severe hypoglycaemic events; a 17% rate reduction in nocturnal hypoglycaemia; no improvement in HbA1c Scenario 3: 28% risk reduction in severe hypoglycaemic events; a 22% rate reduction in nocturnal hypoglycaemia; no improvements in HbA1c. Scenario 4: 0.19%	Scenario 3: Intervention 1: £9,747 Intervention 2: £8,703 Incremental (2-1): £1,043 (CI NR; p = NR) Scenario 4: Intervention 1: £10,084 Intervention 2: £8,713 Incremental (2-1): £1,371 (CI NR; p = NR) Scenario 5: Intervention 1: £9,921 Intervention 2: £8,825 Incremental (2-1): £1,096 (CI NR; p = NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Costs for hypoglycaemia; insulin; insulin delivery; macrovascular events; retinopathy, blindness (severe visual loss), nephropathy, peripheral vascular disease and ketoacidosis.	Intervention 1: 10.99 Intervention 2: 10.84 Incremental (2-1): 0.14 (CI NR; p = NR) Scenario 4: Intervention 1: 10.99 Intervention 2: 10.85 Incremental (2-1): 0.14 (CI NR; p = NR) Scenario 5: Intervention 1: 11.18 Intervention 2: 10.83 Incremental (2-1): 0.34 (CI NR; p = NR)	(£20K/30K threshold): NR Scenario 4: £9,767 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR Scenario 5: £3,189 per QALY gained (pa) CI:NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Deterministic sensitivity analysis was undertaken with the ICER sensitive to the price of glargine; utility decrements of hypoglycaemic events and patients mean weight. The ICER was most sensitive to duration of HbA1c treatment effects. If glargine only has a 2-year treatment effect, given the best improvement of 0.45% used in scenario 5, the ICER increases to £47,445. Apart from this, the mean ICER values remained with the £20K per QALY gained threshold.

	improvement in HbA1c Scenario 5: 0.45% improvement in HbA1c			

Data sources
Health outcomes: Baseline characteristics were taken from the DCCT[491]. Background rates of hypoglycaemia were drawn from two trials[393,491] and a survey[103,104]. Insulin HbA1c effectiveness data came from two meta-analyses[406,408], one of which is unpublished. Hypoglycaemia reductions were taken from two trials[408,437]. **Quality-of-life weights:** UKPDS data which used EQ5D UK tariff utilities and the HODaR database[103,103]. **Cost sources:** British National Formulary 2006, NHS PCA 2005, NHS Reference costs, and trial data.
Comments
Source of funding: Sanofi-Aventis. **Limitations:** One meta-analysis used for the clinical data has not been published, meaning we are unable to appraise the quality; ; the effectiveness data has come from non-inferiority trials and as such has not been powered to detect a difference between the regimens; Framingham data to estimate cardiovascular events is likely to underestimate the rate at which they occur and may lead to an underestimate of costs; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the model does not include subsequent cardiovascular events and the likes of angina and heart failure are not included due to the lack of adequate risk equations, leading to conservative endpoints and estimates as certain costs will be excluded as not all health effects are included within the model. **Other:** The authors conclude that their estimates are likely to be an underestimate of the true cost-effectiveness and that their model is only as good as the data it uses but this was the best data available UK data at that time.
Overall applicability*: Directly applicable Overall quality: Very serious limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; DCCT, Diabetes Control and Complications Trial; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; HODar, Health Outcomes Data Repository; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; MIMS, Monthly Index of Marketed Medicines; NHS PCA, NHS Prescription Cost Analysis; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; UKPDS, UK Prospective Diabetes Survey

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 7: PALMER2004

Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for Type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current Medical Research and Opinion. 2004; 20(11):1729-1746. (Guideline Ref ID PALMER2004)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs)	Population: Adults with type 1 diabetes Cohort settings:	Total costs (mean per patient): Intervention 1: £32,698 Intervention 2: £34,405 Incremental (2-1): £1,707	QALYs (mean per patient): Intervention 1: 9.68 Intervention 2: 9.77 Incremental (2-1): 0.09	ICER (Intervention 2 vs. Intervention 1): £19,285 per QALY gained (pa) CI: Probability Intervention 2 cost-effective (30K

Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for Type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current Medical Research and Opinion. 2004; 20(11):1729-1746. (Guideline Ref ID PALMER2004)				
Study design: Probabilistic decision analytic model Approach to analysis: Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes Perspective: UK NHS Time horizon: Lifetime Treatment effect duration: Lifetime Discounting: Costs = 3.5%; Outcomes = 3.5%	Start age = 39.9 M = 61.1% n=1,000 HbA1c = 8.36% BMI = 25.15 Weight (kg) = 75.35 Duration of diabetes = NR Intervention 1: NPH plus human soluble insulin Intervention 2: Insulin detemir plus insulin aspart	(CI NR; p = NR) Currency & cost year: 2003 UK pounds Cost components incorporated: Insulin costs included cost of delivery devices but not SMBG costs. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity.	(CI NR; p = NR)	threshold): 58% Analysis of uncertainty: Non-parametric bootstrapping was undertaken to generate 1000 ICERs to assess the uncertainty around the mean ICER. At a £30K per QALY threshold, insulin detemir has a 58% probability of being cost-effective compared to NPH. Deterministic sensitivity analysis was undertaken to assess the effect of varying key parameters including HbA1c levels, BMI, rate of major hypoglycaemia events, cost of major hypoglycaemia events, disutility from a hypoglycaemia event, varying discount rates and using different time horizons. The ICER was most sensitive to varying the time horizon. When the time horizon was shortened to 5 years, the ICER increased to £36,885 per QALY gained. All other analyses had ICERs ranging between £8,043 and £26,303 per QALY gained.
Data sources				
Health outcomes: Effectiveness data was taken from an unpublished meta-analysis of four clinical trials[206,218,407,441]. Baseline characteristics were pooled averages across all four trials. Quality-of-life weights: UKPDS data that used the EQ5D UK tariff. Where there are data gaps, other sources were used from Australia and USA. Cost sources: MIMS 2004, NHS PCA, NHS Reference Costs 2003, PSSRU 2003 and previous economic evaluations.				

Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for Type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current Medical Research and Opinion. 2004; 20(11):1729-1746. (Guideline Ref ID PALMER2004)
Comments
Source of funding: Novo Nordisk. Limitations: Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; the meta-analysis used for the clinical data has not been published, meaning we are unable to appraise the quality; the trials included within the meta-analysis lead to a high proportion of male patients, which may bias the results due to differing complication risks between genders; due to the progression of type 1 diabetes, the starting age of this cohort appears high. However, this may have been chosen as the risk equations within the complication modules are applicable for a higher age group; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data was for between 16 week and 6 months; uncertainty around particular key clinical inputs including effectiveness of treatments in reducing HbA1c and reductions in hypoglycaemic events were not explored in a sensitivity analysis; insulin doses used within the analysis were not reported; there was no QALY gain given to a reduction in hypoglycaemic events. This may have reduced the overall benefits of insulin detemir; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. Other: NHS reference costs for certain complications were explicitly not used due to them underestimating the true cost as they were not diabetes specific. One of the studies[406,407] used in the meta-analysis changed title name from in press to full publication, and as such, the references from the study and the ones provided here do not match.
Overall applicability*: Directly applicable Overall quality: Potentially serious limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; MIMS, Monthly Index of Marketed Medicines; NHS PCA, NHS Prescription Cost Analysis; NPH, neutral protamine Hagedorn; NR, not reported; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 8: PALMER2007A

Palmer AJ, Valentine WJ, Ray JA, Foos V, Lurati F, Smith I et al. An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1 diabetes in the UK. Current Medical Research and Opinion. 2007; 23(4):895-901. (Guideline Ref ID PALMER2007A)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY gained) **Study design:** Probabilistic decision analytic model	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 39.1 M = 63.2 n=1,000	**Total costs (mean per patient):** Intervention 1: £39,222 Intervention 2: £40,876 Incremental (2-1): £1,654 (CI NR; p = NR)	**QALYs (mean per patient):** Intervention 1: 6.99 Intervention 2: 7.65 Incremental (2-1): 0.66 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £2,500 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£25K threshold): 95% **Analysis of uncertainty:** Non-parametric

Approach to analysis: Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:** Lifetime **Discounting:** Costs = 3.5%; Outcomes = 3.5%	HbA1c = 8.38% BMI = 24.9 Weight (kg) = 73.8 Duration of diabetes (years) = 15.3 **Intervention 1:** NPH plus human soluble insulin (32.1 and 26.4 IU daily) **Intervention 2:** Insulin detemir plus insulin aspart (28.2 and 26.3 IU daily) Both interventions received twice-daily basal insulin treatment with meal-related bolus insulin. Doses were not reported, but can be taken from the trial.	**Currency & cost year:** 2004 UK pounds **Cost components incorporated:** Insulin costs included the cost of delivery devices but not SMBG costs. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity.		bootstrapping was undertaken to generate 1000 ICERs to assess the uncertainty around the mean ICER. At a £25K per QALY threshold, insulin detemir has a 95% probability of being cost-effective compared to NPH. Deterministic sensitivity analysis was undertaken to assess the effect of varying key parameters including HbA1c levels, BMI, rate of major hypoglycaemia events, cost of major hypoglycaemia events, disutility from a hypoglycaemia event, varying discount rates and using different time horizons. The ICER was most sensitive to varying the effect of HbA1c. When only the effects of changes in HbA1c were taken into account, the ICER increased to £12,598 per QALY gained. All other analyses had ICERs ranging between £1,464 and £3,135 per QALY gained.
Data sources				
Health outcomes: The majority of baseline event and effectiveness data were derived from a single trial[207,208]. Where baseline characteristics required for the simulation were not reported in this trial, information was gathered from further UK specific diabetes populations with similar ages and duration of diabetes. **Quality-of-life weights:** UKPDS and hypoglycaemia data that used the EQ5D UK tariff. **Cost sources:** PSSRU 2003, previous economic evaluations, MIMS 2004.				
Comments				
Source of funding: Novo Nordisk. **Limitations:** The baseline event and clinical effectiveness data was derived from a single trial[207,208], which demonstrated a larger reduction in HbA1c and hypoglycaemic events for insulin detemir than what either previous trials or the NCGCs meta-analysis demonstrated; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trial was for 18 weeks; due to the progression of type 1 diabetes, the starting age of this cohort appears high. However, this may have been chosen as the risk equations within the complication modules are applicable for a higher age group; particular				

complication costs were taken from previous economic evaluations and not calculated from UK sources; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** In all situations, insulin detemir plus insulin aspart is cost-effective compared to NPH plus human soluble insulin; no justification was provided for the range of values used within the sensitivity analyses.

Overall applicability*: Directly applicable **Overall quality**: Potentially serious limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; IU, international units; MIMS, Monthly Index of Marketed Medicines; NPH, neutral protamine Hagedorn; NR, not reported; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 9: PFOHL 2012

M. Pfohl, P. K. Schadlich, F. W. Dippel, and K. C. Koltermann. Health economic evaluation of insulin glargine vs. NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. J Med Econ 15 Suppl 2:14-27, 2012. (Guideline Ref ID PFOHL2012)

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome = QALYs) **Study design:** Discrete event simulation model **Approach to analysis:** Simulation model (CRC DES model) derived from the CORE diabetes model based on the DCCT and meta-regression analysis of combined HbA1c and hypoglycaemia outcomes. It includes two acute complications (hypoglycaemia and ketoacidosis) and five long-term complications (end-stage renal disease, amputation, severe visual loss, acute myocardial	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 35 M = 52.6 Duration of diabetes = 13.4 years HbA1c starting level = 8.8% **Intervention 1:** Neutral protamine Hagedorn ()(29.1 IU daily) – 2.1 injections per day	**Total costs (mean per patient):** Intervention 1: £26,807 Intervention 2: £22,255 Incremental (2-1): saves £4,552 (CI NR; p = NR) **Currency & cost year:** 2009/2010 Euros (presented here as 2010UK pounds‡) **Cost components incorporated:** Insulin costs including acquisition costs, discount of pharmacy to the third party payer, deduction of co-payments, cost of delivery	**QALYs (mean per patient):** Intervention 1: 10.92 Intervention 2: 11.31 Incremental (2-1): 0.39 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** Glargine dominates NPH (pa) CI:NR Probability Intervention 2 dominant : 80.4% **Analysis of uncertainty:** Glargine was still dominant in these scenarios: its effectiveness in HbA1c level or hypoglycaemia events was reduced, time horizon was decreased up to 5 years, discount rate was 0%, 5% or 10%. Glargine was dominant in all the variation of + or – 10% of the following parameters: - acquisition costs - all risk factors - cost offset - event-related treatment costs

infarction, stroke). **Perspective:** German third party payer **Time horizon:** 40 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 3% ; Outcomes = 3%	**Intervention 2:** Insulin glargine (24.5 IU daily) - 1.1 injection per day	devices, test strips, needles and glucose monitoring devices (less frequent monitoring and administration with glargine). Cost of complications (acute and long-term).		- all demographic parameters - risk of events - all disutilities It was not dominant anymore when its effectiveness was varied but with no cost offsets.
Data sources				
Health outcomes: Acute events were derived from DCCT functions and from the CORE model for the ketoacidosis events. Long-term complications were based on the UKPDS risk engine. Efficacy of the treatments was taken from a meta-regression analysis by Mullins et al (2007)[348,348] which included studies that were excluded from our clinical review **Quality-of-life weights:** UK EQ5D data provided directly by the DES model. **Cost sources:** German official prices.				
Comments				
Source of funding: Sanofi-Aventis Deutschland GmbH. **Limitations:** The source of effectiveness data was a meta-regression analysis that included studies that were excluded from our clinical review. UKPDS risk engine which focused exclusively on type 2 diabetes was used for long-term complications. Discounting was performed at a different rate to that required by the NICE reference case. Sensitivity analysis was limited as parameters of the same type were varied together by plus or minus 10%. Distributions for Monte Carlo simulations were not reported.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER, incremental cost-effectiveness ratio; NR, not reported; pa, probabilistic analysis; QALYs, quality-adjusted life years
‡ Converted using 2010 purchasing power parities[382]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 10: PRATOOMSOOT2009

Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in type 1 diabetes in the UK. Diabetic Medicine. 2009; 26(8):803-814. (Guideline Ref ID PRATOOMSOOT2009)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision	**Population:** Adults with type 1 diabetes specific to a UK setting. **Cohort settings:**	**Total costs (mean per patient):** Intervention 1: £72,529 Intervention 2: £70,576 Incremental (2-1): –£1953	**QALYs (mean per patient):** Intervention 1: 7.601 Intervention 2: 7.467 Incremental (2-1): 0.105 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** Insulin lispro is dominant over regular human insulin CI: NR Probability Intervention 2 cost-effective

analytic model **Approach to analysis:** Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes **Perspective:** UK NHS **Time horizon:** 50 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 3.5%; Outcomes = 3.5%	Start age = 37.8 M = 53.5% n=1,000 HbA1c = 9.4% BMI = 25.6 Weight = NR Duration of diabetes (years) = 10.4 **Intervention 1:** Regular human insulin, 32.25 IU (plus basal NPH, 20.25 IU) **Intervention 2:** Insulin lispro, 32.25 IU (plus basal NPH, 20.25 IU)	(CI NR; p = NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Insulin costs included drug costs, cost of delivery devices and SMBG costs. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity.		(£30K threshold): 83.9% **Analysis of uncertainty:** For each analysis 1,000 mean cost and effect pairs, each of 1,000 iterations were calculated for each treatment group. Insulin lispro was dominant over regular human insulin for all sensitivity analyses. In addition, in the base-case analysis, the probability that insulin lispro was more cost-effective than regular human insulin was higher at a £20K threshold than at £30K. The model is most sensitive to changes in HbA1c and rates of hypoglycaemia, although this did not change the final result in this analysis.
Data sources				
Health outcomes: Baseline demographics, complications and medical history were sourced from The Health Improvement Network database[105]. Baseline risk factors were sourced from a variety of relevant sources including a 9-year prospective study of macrovascular complications[461]. The treatment effects utilised were those derived in a Cochrane review[462] **Quality-of-life weights:** EQ-5D UK tariff, for utilities from the UKPDS, along with other sources. **Cost sources:** MIMS, NHS Purchasing and Supply Agency, UKPDS, previous economic evaluations				
Comments				
Source of funding: Eli Lilly, manufactures of insulin lispro **Limitations:** Due to the progression of type 1 diabetes, the starting age of this cohort appears high. However, this may have been chosen as the risk equations within the complication modules are applicable for a higher age group; treatment effectiveness was assumed to be				

maintained over the lifetime of the patient, although trial data has short-term follow-up; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** Authors affiliations were Eli Lilly and IMS.

Overall applicability*: Directly applicable Overall quality: Minor limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS Core Diabetes Model; IU/UI, international units; MIMS, Monthly Index of Medical Specialities; NR, not reported; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, United Kingdom Prospective Diabetes Study
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 11: TUNIS2009

Tunis SL, Minshall ME, Conner C, McCormick J, I, Kapor J, Yale J-F et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. Current Medical Research and Opinion. 2009; 25(5):1273-1284. (Guideline Ref ID TUNIS2009)

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes **Perspective:** Canadian provincial government **Time horizon:** 60 years	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 27.0 M = 54% n=1,000 HbA1c = 8.9% BMI = 23.75 Weight = NR Duration of diabetes (years) = 9 **Intervention 1:** NPH plus insulin aspart (32.6 and 26.9 IU daily) **Intervention 2:** Insulin detemir plus insulin	**Total costs (mean per patient):** Intervention 1: £38,353 Intervention 2: £44,533 Incremental (2-1): £6,181 (CI NR; p = NR) **Currency & cost year:** 2007 Canadian dollars (presented here as 2007 UK pounds‡) **Cost components incorporated:** Insulin costs included the drug costs and cost of delivery devices but not SMBG costs. Complications included are	**QALYs (mean per patient):** Intervention 1: 9.354 Intervention 2: 9.829 Incremental (2-1): 0.475 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £12,989 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective ($CAN40K(£24K) threshold): 56.1% **Analysis of uncertainty:** Non-parametric bootstrapping was undertaken to generate 1000 ICERs to assess the uncertainty around the mean ICER. At a £24K per QALY threshold, insulin detemir has a 56.1% probability of being cost-effective compared to NPH. Deterministic sensitivity analysis was undertaken to assess the effect of varying key parameters including discount rates and utilities for major, moderate and minor hypoglycaemic events. The model was most sensitive to changes in utilities for hypoglycaemic events which when utilities are reduced, the ICER increases up to £107,526 per QALY gained.

Treatment effect duration: Lifetime **Discounting:** Costs = 5%; Outcomes = 5%	aspart (39.9 and 30.6 IU daily) Both interventions received once-daily basal insulin treatment with meal-related bolus insulin. Doses were not reported, but can be taken from the trail (median values at 24 months).	angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity.		
Data sources				
Health outcomes: Baseline characteristics, complications and risk factors were taken from the DCCT[491] and from online sources for Canadian demographics. Treatment effects came from a single trail[48,48]. **Quality-of-life weights:** EQ5D US tariff. **Cost sources:** Nova Scotia pharmacy, optometrist and podiatrist fees 2007; previous economic evaluations, Alberta physician fee schedule 2004, Health costing in Alberta 2006.				
Comments				
Source of funding: Novo Nordisk. **Limitations:** Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; baseline characteristics come from the DCCT[491], which may not be completely representative due to the studies age; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial follow-up was only for 24 months; uncertainty around particular key clinical inputs including effectiveness of treatments in reducing HbA1c and cost of insulin treatments were not explored in a sensitivity analysis; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** This study had two separate cohorts for type 1 and type 2 diabetes; only type 1 has been presented here.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; DCCT, Diabetes Control and Complications Trial; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey

‡ Converted using 2007 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 12: VALENTINE2006

Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine and NPH (Structured abstract). Advances in Therapy. 2006; 23(2):191-207. (Guideline Ref ID VALENTINE2006)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes **Perspective:** US healthcare payer **Time horizon:** 35 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 3%; Outcomes = 3%	**Population:** Adults with type 1 diabetes **Cohort settings:** **Insulin detemir vs. NPH:** Start age = 39 M = 63% n=1,000 HbA1c = 8.38% BMI = 24.9 Weight (kg) = NR Duration of diabetes (years) = 15 **Insulin detemir vs. insulin glargine:** Start age = 40.2 M = 51.3 n=1,000 HbA1c = 8.84% BMI = 25.5 Weight (kg) = NR Duration of diabetes (years) = 17 **Intervention 1:** NPH (twice daily plus human	**Total costs (mean per patient):** Intervention 1: £68,894 Intervention 2: £75,543 Incremental (2-1): £6,649 (CI NR; p = NR) Intervention 2: £68,894 Intervention 3: £70,157 Incremental (2-1): -£1,318 (CI NR; p = NR) **Currency & cost year:** 2005 US dollars (presented here as 2005 UK pounds‡) **Cost components incorporated:** Insulin costs included drug costs, cost of delivery devices and SMBG costs. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract,	**QALYs (mean per patient):** Intervention 1: 7.32 Intervention 2: 8.018 Incremental (2-1): 0.698 (CI NR; p = NR) Intervention 2: 7.242 Intervention 3: 7.719 Incremental (2-1): 0.063 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £9,526 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective ($50K/£30K threshold): 100% **ICER (Intervention 2 vs. Intervention 3):** Insulin detemir dominant over insulin glargine CI: NR Probability Intervention 2 cost-effective ($50K/£30K threshold): 80% **Analysis of uncertainty:** Probabilistic sensitivity analysis was used to assess the uncertainty around the ICER. At a £30K per QALY threshold, insulin detemir has a 100% probability of being cost-effective compared to NPH and an 80% probability of being cost-effective compared to insulin glargine. Deterministic sensitivity analysis was undertaken on key variables such as: change in HbA1c, discount rate, duration of treatment effect, costs of insulin and cost of management of hypoglycaemia. Insulin detemir always remains cost-effective compared to NPH and dominant over insulin glargine in all but one analysis, where the cost of insulin detemir is increased by 15%,

	soluble insulin) **Intervention 2:** Insulin detemir (twice daily plus insulin aspart) **Intervention 3:** Insulin glargine (once daily plus insulin aspart)	hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease severity.		where it is still cost-effective.
Data sources				
Health outcomes: Two randomised clinical trials were included, one comparing insulin detemir and NPH[206,208] and one comparing insulin detemir and insulin glargine[406,407]. **Quality-of-life weights:** UKPDS data that used the EQ5D UK tariff. Where there are data gaps, other sources were used from Australia and USA. **Cost sources:** Medicare list prices, Red Book 2005.				
Comments				
Source of funding: Novo Nordisk. **Limitations:** Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; insulin doses used within the analysis were not reported; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data was for between 18 weeks. However, this was shortened to 5 years in a sensitivity analysis; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources that did not comply with the NICE reference case; a 3% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** The authors state the analysis is from a societal perspective; however the majority of analysis is performed from a healthcare payer perspective.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey

‡ Converted using 2005 purchasing power parities[382]

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 13: VALENTINE2011

Valentine WJ, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scandinavian Journal of Public Health. 2011; 39(1):79-87. (Guideline Ref ID VALENTINE2011)

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome = QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Validated simulation model (IMS-CDM), which models the impact of HbA1c levels on the complications of diabetes **Perspective:** Swedish healthcare payer **Time horizon:** 50 years **Treatment effect duration:** Lifetime **Discounting:** Costs = 3%; Outcomes = 3%	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 35 M = 54.7 n=1,000 HbA1c = 8.3% BMI = 24.7 Weight (kg) = NR Duration of diabetes (years) = 13.0 **Intervention 1:** NPH plus insulin aspart (32.6 and 26.9 IU daily) **Intervention 2:** Insulin detemir plus insulin aspart (39.9 and 30.6 IU daily) Both interventions received once-daily basal insulin treatment with meal-related bolus insulin. Doses were not reported, but can be taken from the trail (median values at 24 months).	**Total costs (mean per patient):** Intervention 1: £66,847 Intervention 2: £98,650 Incremental (2-1): £1,804 (CI NR; p = NR) **Currency & cost year:** 2006 Swedish kronor (presented here as 2006 UK pounds‡) **Cost components incorporated:** Insulin costs included drug costs, cost of delivery devices and SMBG costs. Complications included are angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and simulating nonspecific mortality. Costs are included for all complications and at different stages of disease	**QALYs (mean per patient):** Intervention 1: 7.82 Intervention 2: 8.35 Incremental (2-1): 0.53 (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £3,433 per QALY gained (pa) CI:NR Probability Intervention 2 cost-effective (SEK200K/£20K threshold): 99.9% **Analysis of uncertainty:** Probabilistic sensitivity analysis was used to assess the uncertainty around the ICER. At a £20K per QALY threshold, insulin detemir has a 99.9% probability of being cost-effective compared to NPH. Deterministic sensitivity analyses were carried out on key inputs including, time horizon, discount rates, efficacy of treatments, BMI, hypoglycaemic event rates and baseline patient characteristics. The ICER was most sensitive to changes in HbA1c and hypoglycaemia event rates. This however was unlikely to alter the conclusions on cost-effectiveness.

		severity.		
Data sources				
Health outcomes: Prevalence of these compilations was taken from a Swedish cross-sectional retrospective review. Efficacy of the treatments was taken from a recent head to head trial[48,48]. **Quality-of-life weights:** UKPDS data that used the EQ5D UK tariff. Where there are data gaps, other sources were used. **Cost sources:** Swedish Association of Local Authorities and Regions, previous economic evaluations, Dental and Pharmaceutical Benefits Agency.				
Comments				
Source of funding: Novo Nordisk. **Limitations:** Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial follow-up was only for 24 months; Utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources, which did not comply to the NICE reference case; particular complication costs were based on either mixed populations or type 2 diabetes specific patients; a 3% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations. **Other:** An analysis from a societal perspective was also presented.				
Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**				

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; NPH, neutral protamine Hagedorn; NR, not reported; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey
‡ Converted using 2006 purchasing power parities[382]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Table 14: TA053/WARREN2004

National Institute for Health and Clinical Excellence. Diabetes type 1 and 2: the clinical effectiveness and cost effectiveness of long acting insulin analogues for diabetes. NICE technology appraisal guidance 53. London. National Institute for Health and Clinical Excellence, 2002 *(Guideline Ref ID TA053)*

Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technology Assessment. 2004; 8(45):iii-41. *(Guideline Ref ID WARREN2004)*

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA (health outcome =QALY gained) **Study design:** Deterministic decision analytic model	**Population:** Adults with type 1 diabetes **Cohort settings:** Start age = 27 M = 52.5% n=NR HbA1c = 8.87%	**Total costs (mean per patient):** Intervention 1: £1,738 Intervention 2: £2,311 - £2,554 Incremental (2-1): £573 - £816 (CI NR; p = NR)	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2-1): NR (CI NR; p = NR)	**ICER (Intervention 2 vs. Intervention 1):** £3,496-£4,978 per QALY gained (pa) CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** The model was most sensitive to the utility gained from reducing

Approach to analysis: Model that uses insulin therapies to estimate the incidence of hypoglycaemia and the resultant cost and QALYs, dependant on method of administration. Long-term complications were only taken into consideration in the sensitivity analysis. **Perspective:** UK NHS **Time horizon:** 9 years **Treatment effect duration:** 9 years **Discounting:** Costs = NR; Outcomes = NR	BMI = NR Weight (kg) = NR Duration of diabetes (years) = 5.6 **Intervention 1:** NPH **Intervention 2:** Insulin glargine	**Currency & cost year:** 2001 UK pounds **Cost components incorporated:** Insulin costs (only basal component), cost of severe hypoglycaemic event, (long-term complications in sensitivity analysis).		fear of hypoglycaemia. If the model assumes no utility is gained, the ICER increases to between £389,356 and £554,411, dependant on mode of administration. Other variables are also subject to sensitivity analysis such as introducing a reduction in HbA1c, using different fear assumptions and changing the rate of discounting. Overall, the ICER for ranges from £954 - £554,411, dependant on mode of administration, highlighting considerable uncertainty.
Data sources				
Health outcomes: Baseline data on hypoglycaemic events was taken from a single trial[393,394] whilst effectiveness data on risk reduction was taken from a single trial[419,420] **Quality-of-life weights:** Utility weights for hypoglycaemia was taken from a cost of illness study whilst utility weights for long term complications were taken from the industry submission. **Cost sources:** NHS reference costs 2002, PSSRU 2001, industry submission.				
Comments				
Source of funding: NIHR HTA **Limitations:** The main assumption that insulin glargine has no advantage over NPH for improved HbA1c level is not borne out in our clinical review; cohort characteristics are not detailed in the study but can be calculated from the DCCT[491]; the source of baseline event data has been excluded in the NCGC clinical review; quality-of-life weights are taken from a cost of illness study in children and adolescents and long term weights are taken from the industry submission which is confidential; costs included in the model are limited and costs for long-term complications are taken from the industry submission; the sensitivity analysis appears very limited with no sensitivity analysis undertaken on the variables used in long term complication analysis; all health effects are only taken into account in the sensitivity analysis of the model; discount rates used for costs and QALYs not reported; time horizon is too short to account for all costs and outcomes. **Other:** Only the results of the assessment group analysis is presented here as the majority of the industry submission is confidential and removed from the document.				

The majority of data not reported in the assessment group analysis is due to confidentiality restrictions. Methods of administration are vial, cartridge and pen device.
Overall applicability*: Directly applicable Overall quality: Very serious limitations**

Abbreviations: BMI, body mass index; CI, 95% confidence interval; CUA, cost-utility analysis; DCCT, Diabetes Control and Complications Trial; EQ-5D, Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); HbA1c, glycosylated haemoglobin; HODaR, Health Outcomes Data Repository; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; IMS-CDM, IMS-Centre for Outcomes Research Diabetes Model; NIHR, National Institute of Health Research; NPH, neutral protamine Hagedorn; NR, not reported; PSSRU, Personal Social Services Research Unit; QALYs, quality-adjusted life years; SMBG, self-monitoring of blood glucose; UKPDS, UK Prospective Diabetes Survey
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

H.5 Pancreas transplant and islet cell transplantation

None

H.6 Hypoglycaemia

None

H.7 Ketone monitoring

None

H.8 Arterial risk control

None

H.9 Inpatient management

None

H.10 Complications

None

Appendix I: GRADE tables

I.1 Diagnosis

None

I.2 Education programmes and self-care

I.2.1 Structured education programmes

Table 15: Clinical evidence profile: Structured education programme versus control - usual care or other type of education (less than or equal to 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute	Quality	Importance
HbA1c % (follow-up 6 months; measured with: BGATIII, DAFNE, DeWeert, HYPOS, PRIMAS, Rossi 2010, Rossi 2013, Terent; Better indicated by lower values)												
8	Randomised trials	Very serious[a]	Very serious[b]	No serious indirectness	No serious imprecision[c]	None	779	617	-	MD 0.15 lower (0.27 to 0.03 lower)	VERY LOW	CRITICAL
HbA1c, % - MD only given (follow-up 6 months; measured with: BITES; Better indicated by lower values)												
1	Randomised trials	Very serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	54	60	-	MD 0.06 lower (0.32 lower to 0.2 higher)6	VERY LOW	CRITICAL
HbA1c, % - SD not given (follow-up 6 months; measured with: HAATT; Better indicated by lower values)												
1	Randomised trials	Very serious[g]	No serious inconsistency	No serious indirectness	Very serious8	None	30	30	-	MD 0 higher (0 to 0 higher)9	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute		
Severe hypoglycaemia (episodes/study) (follow-up 6 months; assessed with: DAFNE, Rossi)												
2	Randomised trials	Very serious[j]	No serious inconsistency	No serious indirectness	Very serious[k]	None	12/134 (9%)	11/135 (8.1%)	RR 1.17 (0.56 to 2.48)	14 more per 1000 (from 36 fewer to 121 more)	VERY LOW	CRITICAL
Severe hypoglycaemia (episodes / 6 months) (follow-up 6 months; measured with: BGATIII; Better indicated by lower values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	No serious imprecision[m]	None	56	55	-	MD 0.94 lower (1.7 to 0.18 lower)	LOW	CRITICAL
Severe hypoglycaemia (episodes/month) (follow-up 6 months; measured with: deweerdt; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[n]	None	355	203	-	MD 0.05 higher (0.04 lower to 0.14 higher)	LOW	CRITICAL
Severe hypoglycaemia (episodes/patient year) (follow-up 6 months; measured with: HYPOS, PRIMAS, Rossi 2013; Better indicated by lower values)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[m]	None	219	214	-	MD 0.04 lower (0.37 lower to 0.29 higher)	HIGH	CRITICAL
Severe hypoglycaemia (episodes/person) - SD not given (follow-up 6 months; measured with: HAATT; Better indicated by lower values)												
1	Randomised trials	Very serious[g]	No serious inconsistency	No serious indirectness	Very serious[h]	None	30	30	-	MD 0 higher (0 to 0 higher)15	VERY LOW	CRITICAL
Addqol - impact (follow-up 6 months; measured with: DAFNE; Better indicated by higher values)												
1	Randomised trials	Very serious[j]	No serious inconsistency	No serious indirectness	No serious imprecision[p]	None	67	72	-	MD 0.4 higher (0.34 to 0.46 higher)	LOW	CRITICAL
Addqol - impact and importance (follow-up 6 months; measured with: HYPOS; Better indicated by higher values)												
1	Randomised trials	Very serious[r]	No serious inconsistency	No serious indirectness	No serious imprecision[r]	None	74	72	-	MD 0.1 lower (0.36 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute	Quality	Importance
										0.16 higher)		
DTSQ - total satisfaction (follow-up 6 months; measured with: DAFNE; Better indicated by higher values)												
1	Randomised trials	Very serious[j]	No serious inconsistency	No serious indirectness	No serious imprecision[s]	None	67	72	-	MD 8.76 higher (7.09 to 10.43 higher)	LOW	CRITICAL
SF-36 physical (follow-up 6 months; measured with: Rossi; Better indicated by higher values)												
1	Randomised trials	Serious[t]	No serious inconsistency	No serious indirectness	No serious imprecision[l]	None	67	63	-	MD 0.4 lower (2.53 lower to 1.73 higher)	MODERATE	CRITICAL
SF-36 physical health - MD only given (follow-up 6 months; measured with: BITES; Better indicated by lower values)												
1	Randomised trials	Very serious[d]	No serious inconsistency	No serious indirectness	Very serious[v]	None	54	60	-	MD 2.2 higher (0.7 lower to 5 higher)23	VERY LOW	CRITICAL
SF-36 mental (follow-up 6 months; measured with: Rossi; Better indicated by higher values)												
1	Randomised trials	Serious[t]	No serious inconsistency	No serious indirectness	Serious[y]	None	67	63	-	MD 5 higher (1.09 to 8.91 higher)	LOW	CRITICAL
Hospital admissions (follow-up 6 months; assessed with: Rossi)												
1	Randomised trials	Serious[t]	No serious inconsistency	No serious indirectness	No serious imprecision[y]	None	0/67 (0%)	0/63 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT
Hypoglycaemia unawareness (perceived frequency, scale 0-6) (measured with: DAFNE; range of scores: 0-6; Better indicated by higher values)												
1	Randomised trials	Very serious[j]	No serious inconsistency	No serious indirectness	Serious[z]	None	67	72	-	MD 0.24 lower (0.67 lower to 0.19 higher)	VERY LOW	IMPORTANT
Hypoglycaemia unawareness (> recognition of low blood glucose, % patients) (follow-up 6 months; measured with: BGATIII; range of scores: 0-100; Better indicated by higher values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	Serious[aa]	None	56	55	-	MD 12.40 higher (2.41 to 22.39	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute	Quality	Importance
										higher)		
Hypoglycaemia unawareness (HAQ) (follow-up 6 months; measured with: HYPOS; range of scores: 0-7; Better indicated by lower values)												
1	Randomised trials	Very serious[q]	No serious inconsistency	No serious indirectness	Serious[bb]	None	74	72	-	MD 0.3 lower (0.67 lower to 0.07 higher)	VERY LOW	IMPORTANT
Hypoglycaemia unawareness (VAS) - SD not given (follow-up 6 months; measured with: HYPOS; range of scores: 0-10; Better indicated by higher values)												
1	Randomised trials	Very serious[q]	No serious inconsistency	No serious indirectness	Very serious[cc]	None	74	72	-	MD 0.8 higher (0.2 to 1.4 higher)	VERY LOW	IMPORTANT
Hypoglycaemia unawareness (Change in Clarke score; max score 7) (follow-up 6 months; measured with: PRIMAS; range of scores: 0-7; Better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[dd]	None	81	79	-	MD 0.1 lower (0.52 lower to 0.32 higher)	HIGH	IMPORTANT
Hypoglycaemia unawareness (% detection of low blood glucose) - no SD given (follow-up 6 months; measured with: HAATT; range of scores: 0-100; Better indicated by higher values)												
1	Randomised trials	Very serious[g]	No serious inconsistency	No serious indirectness	Very serious[h]	None	30	30	-	MD 0 higher (0 to 0 higher)31	VERY LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Worry (follow-up 6 months; measured with: BGATIII; range of scores: 0-50; Better indicated by lower values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	No serious imprecision[ff]	None	56	55	-	MD 0.60 higher (3.42 lower to 5.12 higher)	LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Behaviour (follow-up 6 months; measured with: BGATIII; range of scores: 0-85; Better indicated by lower values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	Serious[gg]	None	56	55	-	MD 2.10 higher (0.63 lower to 4.83 higher)	VERY LOW	IMPORTANT
Fear of hypoglycaemia (change in dsqol) (follow-up 6 months; measured with: Rossi 2013; range of scores: 0-66; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[t]	No serious inconsistency	No serious indirectness	No serious imprecision[hh]	None	64	63	-	MD 5.34 lower (12.11 lower to 0.23 higher)	MODERATE	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Worry - MD only given (follow-up 6 months; measured with: BITES; range of scores: 0-50; Better indicated by lower values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	Very serious[h]	None	50	53	-	MD 2.4 lower (7.2 lower to 2.4 higher)	VERY LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Behaviour - MD only given (follow-up 6 months; measured with: BITES; range of scores: 0-85; Better indicated by lower values)												
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	Very serious[h]	None	50	53	-	MD 0.01 lower (2.9 lower to 2.9 higher)	VERY LOW	IMPORTANT
Depression (CES-D) (follow-up 6 months; measured with: HYPOS, PRIMAS; range of scores: 0-60; Better indicated by lower values)												
2	Randomised trials	Serious[ii]	No serious inconsistency	No serious indirectness	No serious imprecision[jj]	None	155	151	-	MD 0.2 lower (0.85 lower to 1.45 higher)	MODERATE	IMPORTANT
Depression (CES-D) - no SD given (follow-up 6 months; measured with: BGAT; range of scores: 0-60; Better indicated by lower values)												
1	Randomised trials	Very serious[kk]	No serious inconsistency	No serious indirectness	Very serious[h]	None	41	45	-	MD 0 higher (0 to 0 higher)38	VERY LOW	IMPORTANT
Anxiety (STAI) (follow-up 6 months; measured with: HYPOS; range of scores: 0-80; Better indicated by lower values)												
1	Randomised trials	Very serious[q]	No serious inconsistency	No serious indirectness	No serious imprecision[mm]	None	74	72	-	MD 0.50 higher (1.54 lower to 2.54 higher)	LOW	IMPORTANT
PAID (follow-up 6 months; measured with: HYPOS; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[q]	No serious inconsistency	No serious indirectness	No serious imprecision[nn]	None	74	72	-	MD 0.70 lower (4.45 lower to 3.05	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control	Relative (95% CI)	Absolute	Quality	Importance
										higher)		
PAID - no SD given (follow-up 6 months; measured with: BGAT; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[kk]	No serious inconsistency	No serious indirectness	Very serious[h]	None	41	45	-	MD 0 higher (0 to 0 higher)41	VERY LOW	IMPORTANT
Knowledge, % correct answers (follow-up 6 months; measured with: Korhonen; range of scores: 0-100; Better indicated by higher values)												
1	Randomised trials	Very serious[p p]	No serious inconsistency	No serious indirectness	No serious imprecision[qq,r r]	None	39	38	-	MD 7.50 higher (6.63 to 8.37 higher)	LOW	IMPORTANT
Knowledge (change score out of 11) (follow-up 6 months; measured with: PRIMAS; range of scores: 0-11; Better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[qq]	None	81	79	-	MD 0.10 higher (0.4 lower to 0.6 higher)	HIGH	IMPORTANT
Adherence, no. of patients (follow-up 6 months; assessed with: PRIMAS)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[ss]	None	1/81 (1.2%)	2/79 (2.5%)	RR 0.49 (0.05 to 5.27)	13 fewer per 1000 (from 24 fewer to 108 more)	LOW	IMPORTANT

(a) Overall balance of evidence across studies: unclear randomisation, inadequate/not mentioned allocation concealment, blinding not mentioned, lack of ITT analysis.
(b) Significant heterogeneity between studies (I2 approx. 75%, p<0.1)
(c) 95% CI does not cross either of the MIDs (MID = ±0.48% , that is,. 0.5 x SD of 0.95)
(d) Overall balance of evidence across studies: Unclear randomisation, inadequate allocation concealment, blinding not mentioned
(e) Number of events in each arm was not reported - only the MD was provided; 95% CI does not cross either of the MIDs (MID = ±0.66 that is, 0.5 x SD of 1.32)
(f) study reported p=0.67
(g) Overall balance of evidence across studies: Unclear randomisation, allocation concealment not mentioned, blinding not mentioned
(h) SD not given therefore unable to calculate MD and 95% CI
(i) Data provided for HbA1c: HAATT 8.0% and SMBG 8.1%
(j) Overall balance of evidence across studies: inadequate allocation concealment, blinding not mentioned, no ITT analysis
(k) 95% CI crosses both MIDs (0.75 and 1.25)

(l) Overall balance of evidence across studies: inadequate randomisation, allocation concealment not mentioned, blinding not mentioned, No ITT analysis, high dropouts (>20%), selective outcome reporting
(m) 95% CI does not cross either of the MIDs (MID = ±1.0 that is, 0.5 x SD of 2.0)
(n) 95% CI does not cross either of the MIDs (MID = ±0.45% that is 0.5 x SD of 0.9)
(o) Data given: HAAT 0.4, SMBG 1.7; p=0.03
(p) 95% CI does not cross either of the MIDs (MID = ±1.0 that is, 0.5 x SD of 2.0)
(q) Overall balance of evidence across studies: unclear randomisation, allocation concealment not mentioned, blinding not mentioned, no ITT analysis
(r) 95% CI does not cross either MID (MID = ±0.4 that is, 0.5 x SD of 0.8)
(s) 95% CI does not cross either of the MIDs (MID = ±2.48 that is, 0.5 x SD of 4.95)
(t) Overall balance of evidence across studies: unclear randomisation, inadequate blinding,
(u) 95% CI does not cross either of the MIDs (established MID = ±3.0)
(v) Number of events in each arm was not reported - only the MD was provided; 95% CI crosses one of the MIDs (established MID = ±3.0)
(w) Study reported p=0.14
(x) 95% CI crosses one of the MIDs (established MID = ±3.0)
(y) Zero event rates in each arm
(z) 95% CI crosses one of the MIDs (MID = ±0.65% that is, 0.5 x SD of 1.3)
(aa) 95% CI crosses one of the MIDs (MID = ±13.4 that is, 0.5x SD of 26.8)
(bb) 95% CI crosses one of the MIDs (MID = ±0.6 that is, 0.5 x SD of 1.2)
(cc) No SDs were provided so MIDs inestimable. Only the means and MD was provided.
(dd) 95% CI does not cross either of the MIDs (MID = ±0.65 that is, 0.5 x SD of 1.3)
(ee)Data provided for detection of low blood Glucose: HAATT 70% and SMBG 55%, p=0.005
(ff) 95% CI does not cross either of the MIDs (MID = ±6.1 that is, 0.5 x SD of 12.2)
(gg) 95% CI crosses one of the MIDs (MID = ±3.7 that is, 0.5 x SD of 7.3)
(hh) 95% CI does not cross either of the MIDs (MID= 8.9 that is, 0.5 x SD of 17.7)
(ii) Overall balance of the evidence: some issues in half of the evidence base with randomisation, allocation concealment and blinding.
(jj) 95% CI does not cross either of the MIDs (MID = ±3.55 that is, 0.5 x SD of 7.1)
(kk) Overall balance of evidence across studies: Unclear randomisation, allocation concealment not mentioned, blinding not mentioned, >20% drop-outs
(ll) Data provided for Depression (CES-D): BGAT 15.8 and Control 13.5, p=0.74
(mm) 95% CI does not cross either of the MIDs (MID = ±3.15 that is, 0.5 x SD of 6.3)
(nn) 95% CI does not cross either of the MIDs (MID = ±11.6 that is, 0.5 x SD of 5.8)
(oo) Data provided for PAID: BGAT 44.4 and Control 38.7, p=0.99
(pp) Overall balance of evidence across studies: unclear randomisation, unclear allocation concealment, inadequate blinding
(qq) 95% CI does not cross either of the MIDs (MID = ±0.8 that is, 0.5 x SD of 1.6)
(rr) 95% CI does not cross either of the MIDs
(ss) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)

Table 16: Clinical evidence profile: Structured education programme versus control - usual care or other type of education (>6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control (≥12 months follow-up)	Relative (95% CI)	Absolute	Quality	Importance
HbA1c % (follow-up 12 months; measured with: BGATIII, deweert, Terent, Trento 2005, Trento 2011; Better indicated by lower values)												
5	Randomised trials	Very serious[a]	Serious[a]	No serious indirectness	No serious imprecision[b]	None	153	147	-	MD 0.08 higher (0.01 lower to 0.17 higher)	VERY LOW	CRITICAL
HbA1c % (between 6 and 12 months) (follow-up 6-12 months; assessed with: BGAT - Snoek)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	-	0%	-5	-	VERY LOW	CRITICAL
HbA1c, % - MD only given (follow-up 12 months; measured with: BITES; Better indicated by lower values)												
1	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	Serious[g]	None	54	60	-	MD 0.01 higher (0.3 lower to 0.32 higher)8	VERY LOW	CRITICAL
Severe hypoglycaemia (episodes/study) (follow-up 12 months; assessed with: Trento)												
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Very serious[j]	None	5/27 (18.5%)	6/29 (20.7%)	RR 0.9 (0.31 to 2.6)	21 fewer per 1000 (from 143 fewer to 331 more)	VERY LOW	CRITICAL
Severe hypoglycaemia (episodes/6 months) (follow-up 12 months; measured with: BGATIII; Better indicated by lower values)												
1	Randomised trials	Very serious[k]	No serious inconsistency	No serious indirectness	Serious[l]	None	56	55	-	MD 1.65 lower (2.86 to 0.44 lower)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control (≥12 months follow-up)	Relative (95% CI)	Absolute	Quality	Importance
Severe hypoglycaemia (episodes/12 months) - SD not given (follow-up 12 months; measured with: BITES; Better indicated by lower values)												
1	Randomised trials	Very seriou[f]	No serious inconsistency	No serious indirectness	Very serious[m]	None	54	60	-	MD 0.05 lower (0.61 lower to 0.5 higher)14	VERY LOW	CRITICAL
Severe hypoglycaemia (episodes/person) - SD not given (follow-up 18 months; measured with: HAATT; Better indicated by lower values)												
1	Randomised trials	Very serious[o]	No serious inconsistency	No serious indirectness	Very serious[p]	None	30	30	-	MD 0 higher (0 to 0 higher)17	VERY LOW	CRITICAL
Dqol (follow-up 12 - 36 months; measured with: Trento 2005; Trento 2011; Better indicated by lower values)												
2	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	No serious imprecision[r]	None	57	57	-	MD 2.40 lower (3.13 to 1.67 lower)	LOW	CRITICAL
SF-36 physical health - MD only given (follow-up 12 months; measured with: BITES; Better indicated by lower values)												
1	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	Very serious[s]	None	54	60	-	MD 1.9 higher (0.8 lower to 4.6 higher)20	VERY LOW	CRITICAL
Hypoglycaemia unawareness (> recognition of low blood glucose, % patients) (follow-up 12 months; measured with: BGATIII; range of scores: 0-100; Better indicated by higher values)												
1	Randomised trials	Very serious[o]	No serious inconsistency	No serious indirectness	Serious[u]	None	56	55	-	MD 17.2 higher (7.77 to 26.63 higher)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control (≥12 months follow-up)	Relative (95% CI)	Absolute	Quality	Importance
Fear of hypoglycaemia (Hypo fear survey) - Worry (follow-up 12 months; measured with: BGATIII; range of scores: 0-50; Better indicated by lower values)												
1	Randomised trials	Very serious[k]	No serious inconsistency	No serious indirectness	Serious[v]	None	56	55	-	MD 1.50 lower (5.78 lower to 2.78 higher)	VERY LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Behaviour (follow-up 12 months; measured with: BGATIII; range of scores: 0-85; Better indicated by lower values)												
1	Randomised trials	Very serious[k]	No serious inconsistency	No serious indirectness	No serious imprecision[w]	None	56	55	-	MD 0.60 lower (3.48 lower to 2.28 higher)	LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Worry- MD only given (follow-up 12 months; measured with: BITES; range of scores: 0-50; Better indicated by lower values)												
1	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	Very serious[m]	None	50	52	-	MD 1.4 lower (6.2 lower to 3.4 higher)	VERY LOW	IMPORTANT
Fear of hypoglycaemia (Hypo fear survey) - Behaviour - MD only given (follow-up 12 months; measured with: BITES; range of scores: 0-85; Better indicated by lower values)												
1	Randomised trials	Very serious[f]	No serious inconsistency	No serious indirectness	Very serious[m]	None	50	52	-	MD 1.2 lower (4.2 lower to 1.9 higher)	VERY LOW	IMPORTANT
Depression (CES-D) - no SD given (follow-up 12 months; measured with: BGAT; range of scores: 0-60; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[x]	None	41	45	-	MD 0 higher (0 to 0	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Structured education	Control (≥12 months follow-up)	Relative (95% CI)	Absolute	Quality	Importance
										higher)25		
PAID - no SD given (follow-up 12 months; measured with: BGAT; range of scores: 0-100; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[p]	None	41	45	-	MD 0 higher (0 to 0 higher)27	VERY LOW	IMPORTANT
Knowledge, % correct answers (follow-up 12 months; measured with: Korhonen, Lennon; range of scores: 0-100; Better indicated by higher values)												
2	Randomised trials	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision[cc]	None	39	38	-	MD 7.50 higher (6.63 to 8.37 higher)	LOW	IMPORTANT
Knowledge of diabetes (GISED) (follow-up 12-36 months; measured with: Trento 2005, Trento 2011; range of scores: 0-11; Better indicated by higher values)												
2	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	No serious imprecision[z]	None	57	57	-	MD 1.14 higher (1.04 to 1.23 higher)	LOW	IMPORTANT

(a) Significant heterogeneity: I2 >75%, p<0.1
(b) 95% CI does not cross either of the MIDs (MID = ±0.73 ie. 0.5 x SD of 1.45)
(c) Overall balance of evidence across studies: Unclear randomisation, allocation concealment not mentioned, blinding not mentioned, >20% drop-outs
(d) Number of events in each arm was not reported, therefore the RR and 95% CI were not estimable
(e) Study reported that there was NS change in either of the groups
(f) Overall balance of evidence across studies: Unclear randomisation, inadequate allocation concealment, blinding not mentioned
(g) Number of events in each arm was not reported - only the MD was provided; 95% CI does not cross either of the MIDs (MID = ±0.66 ie. 0.5 x SD of 1.32)
(h) study reported p=0.94
(i) Overall balance of evidence across studies: unclear randomisation, allocation concealment not mentioned, blinding not mentioned
(j) 95% CI crosses both of the MIDs (MID = 0.75 and 1.25)
(k) Overall balance of evidence across studies: inadequate randomisation, allocation concealment not mentioned, blinding not mentioned, No ITT analysis, high dropouts (>20%), selective outcome reporting
(l) 95% CI crosses one of the MIDs (MID = ±1.8 ie. 0.5 x SD of 3.6)

(m) SD was not provided, only the MD was given. Therefore the MID could not be calculated.
(n) Study reported p=0.85
(o) Overall balance of evidence across studies: Unclear randomisation, allocation concealment not mentioned, blinding not mentioned
(p) SD not given therefore unable to calculate MD and 95% CI
(q) Data provided for severe hypo: HAATT 1.76 and SMBG 3.65; p<0.023
(r) 95% CI does not cross either of the MIDs (MID = ±5.4 ie. 0.5 x SD of 10.85)
(s) Number of events in each arm was not reported - only the MD was provided; 95% CI crosses one of the MIDs (established MID = ±3.0)
(t) Study reported p=0.14
(u) 95% CI crosses one of the MIDs (MID = ±12.7 ie. 0.5x SD of 25.4)
(v) 95% CI crosses one of the MIDs (MID = ±5.7 ie. 0.5 x SD of 11.4)
(w) 95% CI does not cross either of the MIDs (MID = 3.9 ie. 0.5 x SD of 7.7)
(x) SD not given therefore unable to calculate MD and 95% CI
(y) Data provided for Depression (CES-D): BGAT 15.5 and Control 15.4, p=0.19
(z) 95% CI does not cross either of the MIDs (MID = ±0.08 ie. 0.5 x SD of 0.15)
(aa) Data provided for PAID: BGAT 45.4 and Control 38.3, p=0.68
(bb) Overall balance of evidence across studies: unclear randomisation, unclear allocation concealment, inadequate blinding
(cc) 95% CI does not cross either of the MIDs (MID = ±1.2 ie. 0.5 x SD of 2.4)

I.2.2 Dietary management

I.2.2.1 Carb counting

Table 17: Clinical evidence profile: Carbohydrate counting versus no carbohydrate counting (RCTs)

Quality assessment							No of patients		Effect			
No. Studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Carb counting	No carb counting	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (%) > 6 months (final values) (follow-up 9 months; Better indicated by lower values) [SCAVONE2010]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	73	156	-	MD 0.1 lower (0.41 lower to 0.21 higher)(c)	LOW	CRITICAL
HbA1c (%) ≤ 6 months (final values) (follow-up 16 weeks; Better indicated by lower values) [SCHMIDT2012]												
1(d)	Randomised trials	No serious risk of	No serious inconsistency	No serious indirectness	Serious[f]	None	21	8	-	MD 0.5 lower (1.35	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No. Studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Carb counting	No carb counting	Relative (95% CI)	Absolute		
		bias[e]								lower to 0.35 higher)		
Mild hypoglycaemia > 6 months (follow-up 9 months. Control group risk 7.1%; assessed with: SMBG [BG<3.9mmol/litre]) [SCAVONE2010]												
1(d)	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[g]	None	3/73 (4.1%)	11/156 (7.1%)	RR 0.58 (0.17 to 2.03)	30 fewer per 1000 (from 59 fewer to 73 more)	VERY LOW	CRITICAL
Severe hypoglycaemia ≤ 6months (follow-up range 16-24 weeks; median control group risk 6.25%; assessed with: hypoglycaemia requiring assistance) [SCHMIDT2012; LAURENZI 2011]												
2	Randomised trials	No serious risk of bias[e]	No serious inconsistency	No serious indirectness	Very serious[g]	None	2/51 (3.9%)	6.25%	RR 0.76 (0.08 to 7.29)	15 fewer per 1000 (from 58 fewer to 393 more)	LOW	CRITICAL
DSQOLS (Diet restrictions) ≤ 6 months (follow-up 24 weeks; data reported as change from baseline (median and IQR); measured with: Diabetes specific QOL scale (DSQOLS); Better indicated by higher values) [LAURENZI2011]												
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious[i]	None	28	28	-	SS higher (P=0.008 reported; median change score 5.5 vs. 0)(j)	LOW	IMPORTANT
DSQOLS (Social relations; Leisure-time flexibility; Physical complaints; Worries about the future; Daily hassles) ≤ 6 months; follow-up 24 weeks; data reported as change from baseline (median and IQR); measured with: Diabetes specific QOL scale (DSQOLS); Better indicated by higher values) [LAURENZI2011]												
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious[i]	None	28	28	-	NS difference between groups (k)	LOW	IMPORTANT
QOL (HFS) <6months (follow-up 16 weeks; measured with: Hypoglycaemia fear survey; transformed onto 0-100 scale; higher scores indicate more fear) [SCHMIDT2012]												
1	Randomised trials	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[m]	None	21	8	-	MD 1.7 lower (15.62	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No. Studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Carb counting	No carb counting	Relative (95% CI)	Absolute	Quality	Importance
										lower to 12.22 higher)		
QOL (PAID) <6months (follow-up 16 weeks; measured with: Problem areas in diabetes questionnaire; transformed onto 0-100 scale; higher scores indicate more problems) [SCHMIDT2012]												
1	Randomised trials	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[n]	None	21	8	-	MD 0.8 higher (14.6 lower to 16.2 higher)	VERY LOW	IMPORTANT
QOL (addqol) <6months (follow-up 16 weeks; measured with: Audit of Diabetes Dependent QOL questionnaire; present QOL scored -9 to 9; higher values indicate better QOL) [SCHMIDT2012]												
1	Randomised trials	Serious[l]	No serious inconsistency	No serious indirectness	Very serious[o]	None	21	8	-	MD 0.4 lower (1.33 lower to 0.53 higher)	VERY LOW	IMPORTANT
QOL (DTSQ) <6months (follow-up 16 weeks; measured with: Diabetes Treatment Satisfaction Questionnaire ; range of scores: 0-36; Better indicated by higher values) [SCHMIDT2012]												
1	Randomised trials	Serious[l]	No serious inconsistency	No serious indirectness	Serious[p]	None	21	8	-	MD 2.1 lower (6.47 lower to 2.27 higher)	LOW	IMPORTANT

(a) Information is from one study at very high risk of bias - allocation concealment unclear; baseline difference comparable to effect estimate; no blinding (objective outcome); missing data >20% between groups (intervention 27%; control 0%); no ANCOVA

(b) 95% CI does not cross either of the default MIDs (95% CI for SMD used as only one study: -0.35 to 0.2; MID = ±0.5)

(c) Reported as SS difference between groups for change score (not enough data provided to report change scores in meta-analysis and GRADE)

(d) HbA1c change scores and mild hypoglycaemia reported as NS different between groups for Laurenzi 2011 but not enough data reported from Laurenzi 2011 to include data in meta-analysis

(e) Information is from studies at low risk of bias

(f) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.33 to 0.32; MID = ±0.5)

(g) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)

(h) Information is from one study at high risk of bias - no blinding (subjective outcome)

(i) Data reported as median (IQR) so unable to calculate CIs and MIDs

(j) SS higher (P=0.008 reported; median change score 5.5 versus 0)

(k) NS difference between groups

(l) Information is from one study at high risk of bias (no blinding - subjective outcome)
(m) 95% CI crosses both of the default MIDs (95% CI for SMD used as only one study: -0.92 to 0.71; MID = ±0.5)
(n) 95% CI crosses both of the default MIDs (95% CI for SMD used as only one study: -0.77 to 0.86; MID = ±0.5)
(o) 95% CI crosses both the default MIDs (95% CI for SMD used as only one study: -1.09 to 0.55; MID = ±0.5)
(p) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.17 to 0.47; MID = ±0.5)

Table 18: Clinical evidence profile: Bolus calculator versus manual carbohydrate counting (RCTs)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Bolus Calculator**	**Carb count**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c (%) ≤ 6 months (follow-up 16-26 weeks; median control group value 8.1%; Better indicated by lower values) [MAURIZI2011, SCHMIDT2012, ZIEGLER2013]												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	147	154	-	MD 0.25 lower (0.41 to 0.08 lower)	MODERATE	CRITICAL
Mild hypoglycaemia ≤ 6 months (follow-up 26 weeks; median CGR 27.4%; assessed with: no. of patients reporting BG <70mg/dl) [ZIEGLER2013]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	43/105 (41%)	27.4%	RR 1.49 (1.02 to 2.18)	134 more per 1000 (from 5 more to 323 more)	LOW	CRITICAL
Severe hypoglycaemia ≤ 6 months (follow-up 16-26 weeks; median CGR 7.9%; assessed with: episode of hypoglycaemia requiring third party assistance (or BG <36mg/dl for Ziegler study)) [SCHMIDT2012, ZIEGLER2013]												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	13/127 (10.2%)	7.9%	RR 1.52 (0.67 to 3.43)	41 more per 1000 (from 26 fewer to 192 more)	VERY LOW	CRITICAL
QOL (HFS) ≤ 6 months (follow-up 16 weeks; measured with: Hypoglycaemia fear survey; transformed onto 0-100 scale; higher scores indicate more fear) [SCHMIDT2012]												
1	Randomise d trials	Serious[e]	No serious inconsistency	No serious indirectness	Very serious[f]	None	22	21	-	MD 0.2 lower (9.34 lower to 8.94 higher)	VERY LOW	IMPORTANT
QOL (PAID) ≤ 6 months (follow-up 16 weeks; measured with: Problem areas in diabetes questionnaire; transformed onto 0-100 scale; higher scores indicate more problems) [SCHMIDT2012]												
1	Randomised trials	Serious[e]	No serious inconsistency	No serious indirectness	Serious[g]	None	22	21	-	MD 2.4 lower (12.81 lower to	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bolus Calculator	Carb count	Relative (95% CI)	Absolute	Quality	Importance
										8.01 higher)		
QOL (addqol) ≤ 6 months (follow-up 16 weeks; measured with: Audit of Diabetes Dependent QOL questionnaire; present QOL scored -9 to 9; higher values indicate better QOL) [SCHMIDT2012]												
1	Randomised trials	Serious[e]	No serious inconsistency	No serious indirectness	Very serious[h]	None	22	21	-	MD 0 higher (0.96 lower to 0.96 higher)	VERY LOW	IMPORTANT
QOL (DTSQ) ≤ 6 months (follow-up 16-26 weeks; measured with: Diabetes Treatment Satisfaction Questionnaire ; range of scores: 0-36; Better indicated by higher values) [SCHMIDT2012]												
1	Randomised trials	Serious[e]	No serious inconsistency[j]	No serious indirectness	Serious[k]	None	22	21	-	MD 5.10 higher (2.19 to 8.01 higher)	LOW	IMPORTANT

(a) The majority of the evidence was from studies at high risk of bias (Ziegler study 78% weighting; randomisation and allocation concealment unclear)
(b) 95% CI does not cross either of the default MIDs (MID = ±0.54 ie. 0.5 x SD of 1.07)
(c) 95% CI crosses the lower default MID (MIDs = 0.75 and 1.25)
(d) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)
(e) Information is from one study at high risk of bias (no blinding - subjective outcome)
(f) 95% CI crosses both default MIDs (95% CI for SMD used as only one study: -0.61 to 0.59; MID = ±0.5)
(g) 95% CI crosses the lower of the default MID (95% CI for SMD used as only one study: -0.73 to 0.46; MID = ±0.5)
(h) 95% CI crosses both of the default MIDs (95% CI for SMD used as only one study: -0.6 to 0.6; MID = ±0.5)
(i) The majority of the evidence was from studies at very high risk of bias (Ziegler study 78% weighting; randomisation and allocation concealment unclear; no blinding - subjective outcome)
(j) I2 = 60% but CIs overlap and effect estimate in same direction
(k) 95% CI crosses the upper default MID (95% CI for SMD used as only one study: -0.40 to 1.68; MID = ±0.5)

I.2.3 Glycaemic index

Table 19: Clinical evidence profile: Low GI diet versus high GI diet

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low GI diet	High GI diet	Relative (95% CI)	Absolute	Quality	Importance
Mean HbA1c (%) – Follow-up at ≤6 months (better indicated by lower values) – Non-RCT: **Calle-Pascual 1988**												
1	Non-randomised crossover study	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	12	12	-	MD 0.25 higher (from 0.09 to 0.59 higher)	VERY LOW	CRITICAL
Mean HbA1c (%) – Follow-up at ≤6 months (better indicated by lower values) - RCTs: **Fontvieille 1992, Venhaus 1988**												
2	RCT	Serious[a]	No serious inconsistency	Serious[c]	No serious imprecision	None	28	28	-	MD 0.36 higher (from 0.14 lower to 0.86 higher)	LOW	CRITICAL
Mean HbA1c (%) – Follow-up at >6 months (better indicated by lower values): **McCulloch 1985**												
1	RCT	Very serious[a]	No serious inconsistency	Serious[d]	Serious[b]	None	12	10	-	MD 0.5 higher (0.08 to 0.92 higher)	VERY LOW	CRITICAL
Severe hypoglycaemia (number of episodes) Follow-up at ≤6 months: **Lafrance 1998, Venhaus 1988**												
2	RCT	Very serious[a]	Serious[(e)]	No serious indirectness	No serious imprecision	None	19	19	-	Not pooled 0 event in total	VERY LOW	CRITICAL
Adherence to treatment (definition 2[(g)]) Follow-up at >6 months: **McCulloch 1985**												
1	RCT	Very serious[a]	No serious inconsistency	Serious[f]	N/A[g]	None	29.8%[(g)] (SEM=6.7)	28.1%[(g)] (SEM=11.7)	N/A	N/A	VERY LOW	IMPORTANT

(a) Several methodological uncertainties were identified (refer to Appendix E for breakdown of risk of bias for each study).
(b) The imprecision was downgraded by one increment if the CI span across two MID zones. It was downgraded by two increments if the CI span across three MID zones.

(c) Fontvieille 1992 reported results of both type 1 diabetes and type 2 diabetes groups. The reason for inclusion of this study is that majority of the study participants had type 1 diabetes and there were no statistically significant differences in results between the two groups.
(d) The intervention group was instructed to consume high carbohydrate (polysaccharides), high fibre, unprocessed foods, and higher intake of vegetables and fruits, whilst the comparison group was instructed to continue with their 'current diet'. This is strictly not the comparison set out by the protocol.
(e) There were differences between the two studies in terms of populations, interventions and follow-up times.
(f) Details of randomisation and allocation concealment have not been given.
(g) McCulloch 1985 reported adherence to treatment in terms of coefficient of variation (SD/mean x 100), based on the participants' self-reported food records.

I.3 Blood glucose

I.3.1 HbA1c

Table 20: Clinical evidence profile; optimum HbA1c target

Study	Design	Results	Limitations	Inconsistency	Indirectness	Imprecision	Importance	Quality
Outcome: Cardiovascular event								
Pittsburgh EDC 2003[381,381]	Case series	See Table 19	VS[a]	N	N	Not estimable	IMPORTANT	Very low
Lehto 1999[288,288]	Case series							
WESDR 1994[344,346]	Case series							
EDIC 2005[350,351]	Case series							
Hypoglycaemia								
Pirez Mendez 2007[397,397]	Case series	See Table 19	VS[b]	N	N	Not estimable	IMPORTANT	Very low
Wikblad 1996[524,525]	Case series							
Lower extremity arterial disease								
WESDR 1999[344,345]	Case series	See Table 19	VS[c]	N	N	Not estimable	CRITICAL	
Pittsburgh EDC 2002[380,380]	Case series							
Quality of life								
Hislop 2008[213,213]	Cross section	See Table 19	VS[d]	N	N	Not estimable	CRITICAL	Very low
Lustman 2005 [299,299]	Cross-section							
Shaban 2006[453,453]	Cross-section							
Tabaei 2004[486,486]	Cross-section							
WESDR 1998[255,260]	Cross-section							
Wikblad 1991[525,525]	Case-series							
Van Tilburg 2001[507]	Cross-section							
Nephropathy								
DCCT 1996[6] DCCT 1993[490]	RCT	See Table 19	VS[e]	N	N	Not estimable	CRITICAL	Very low
Agardh 1997 [23,23]	Case series							
Diamante 1997[125,125]	Cross section							

Wikblad 1991[525,525]	Case series							
SDIS1995 [423-425]	RCT							
WESDR 1995[256,257]	Case series							
Neuropathy								
DCCT 1996[6] DCCT 1993[490]	RCT	See Table 19	S[f]	N	N	Not estimable	CRITICAL	Low
SDIS 1995[423-425]	RCT							
WESDR 1995[256,257]	Case series							
Retinopathy								
Agardh 1997 [23,23]	Case series	See Table 19	VS[g]	N	N	Not estimable	CRITICAL	Very low
Brinhmann-Hansen 1992[67]	Case series							
DCCT 1996[6] DCCT 1993[490]	RCT							
DCCT/EDIC[519,520]	Case Series							
SDIS 1995[423-425]	RCT							
WESDR 1995[256,257]	Case series							
WESDR 1998a[258,260]	Case series							
Wikblad 1991[525,525]	Case series							

Abbreviations: N, not serious; S, serious; VS, very serious
(a) 4/4 studies case series at high risk of bias
(b) 2/2 studies case series at high risk of bias
(c) 2/2 studies case series at high risk of bias
(d) 6/7 studies cross-sectional observation study at high risk of bias, 1/7 studies case series at high risk of bias
(e) 4/6 studies case series at high risk of bias
(f) 1/3 studies case series at high risk of bias
(g) 6/8 studies cross-sectional observation study at high risk of bias

Table 21: Clinical evidence profile; HbA1c frequency of monitoring

Study	Design	Results	Limitations	Inconsistency	Indirectness	Imprecision	Importance	Quality
HbA1c levels								
Larsen 1990[278,278]	RCT	See Table 20	VS[a]	NS	N	Not estimable	CRITICAL	Very low
Fluctuations in HbA1c								
Eid Fares 2010[145,145]	Case series	See Table 20	VS[b]	N	S (iii)	Not estimable	LESS IMPORTANT	Very low
Nephrology								
Eid Fares 2010[145,145]	Case series	See Table 20	VS[c]	N	N	Not estimable	CRITICAL	Very low

Abbreviations: N, not serious; S, serious; VS, very serious
(a) Unclear randomisation, unclear allocation concealment
(b) Case series at very high risk of bias
(c) Indirect outcome

I.3.2 SMBG – frequency and timing

None

I.3.3 SMBG – glucose targets

None

I.3.4 SMBG – technologies

Table 22: Clinical evidence profile: bolus calculator versus no technology for SMBG (less than 6 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bolus calculator	Standard bolus	Relative (95% CI)	Absolute		
HbA1c (%) (follow-up < 6 months; Better indicated by lower values); SCHMIDT 2012												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	None	22	8	-	MD 0.60 lower (1.40 lower to 0.20 higher)	MODERATE	CRITICAL
Hypoglycaemia Fear Survey (HFS) - (0-100 scale) – higher scores indicate more fears (follow-up < 6 months; Better indicated by lower values); SCHMIDT 2012												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[a]	None	22	8	-	MD 1.48 lower (9.07 lower to 6.11 higher)	LOW	IMPORTANT
Problem Areas In Diabetes (PAID) - (0-100 scale) – higher scores indicate more problems (follow-up 6 months; Better indicated by lower values); SCHMIDT 2012												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[e]	None	22	8	-	MD 3.6 lower (19.54 lower to 12.34 higher)	MODERATE	IMPORTANT
Audit of Diabetes-Dependent qol (addqol) - Total (-9 to 9) - higher scores indicate positive impact (follow-up < 6 months; Better indicated by higher values); SCHMIDT 2012												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[e]	None	22	8	-	MD 0.2 lower (1.39 lower to 0.99 higher)	MODERATE	CRITICAL
Severe Hypoglycaemia (follow-up < 6 months); SCHMIDT 2012												
1	Randomised trials	No serious risk of bias[c]	No serious inconsistency	No serious indirectness	Very serious[b]	None	2/22 (9.1%)	1/8 (12.5%)	RR 0.73 (0.08 to 6.97)	34 fewer per 1000 (from 115 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Bolus calculator	Standard bolus	Relative (95% CI)	Absolute		
										746 more)		
Hypoglycaemic event/week (follow-up < 6 months; Better indicated by lower values); GROSS 2003												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	49	49	-	MD 0.3 lower (1.49 lower to 0.89 higher)	MODERATE	CRITICAL
Adverse events (follow-up < 6 months); GROSS 2003												
1	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision 4	None	0/49 (0%)	0/49 (0%)	Not pooled	Not pooled	MODERATE	IMPORTANT

(a) Confidence interval crosses both ends of default MID (0.5 x SD)
(b) Confidence interval crosses both ends of default MID (0.75, 1.25)
(c) Randomisation and allocation concealment unclear
(d) MID not estimable
(e) Confidence interval crosses one end of default MID (0.5 x SD)

I.3.5 Blood glucose monitoring – SMBG versus CGM

Table 23: Clinical evidence profile: retrospective CGM versus SMBG

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Retrospective CGM	SMBG	Relative (95% CI)	Absolute		
Change in HbA1c – Follow-up ≤6 months (Better indicated by lower values)												
2 Chico 2003; Tanenberg	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[b]	None	91	89	-	MD 0.09 lower (0.44 lower to 0.26	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Retrospective CGM	SMBG	Relative (95% CI)	Absolute	Quality	Importance
2004										higher)		
Percentage change in HbA1c – Follow-up > 6 months (Better indicated by lower values)												
1 Newman 2009	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[c]	None	53	52	-	MD 2.60 lower (7.35 lower to 2.15 higher)	HIGH	CRITICAL
Severe hypoglycaemia – Follow-up ≤6 months												
1 Tanenberg 2004	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[d]	None	1/51 (2%)	1/58 (1.7%)	RR 1.14 (0.07 to 17.72)	2 more per 1000 (from 16 fewer to 288 more)	LOW	CRITICAL

(a) 18% (11/62) in CGM versus 12% (8/66) in control group did not complete treatment for Chico 2003
(b) MID = Median SD across control group multiplied by 0.5 (0.56)
(c) MID = Median SD of the control group multiplied by 0.5 (7.4)
(d) Confidence interval crosses both default MIDs (0.75, 1.25)

Table 24: Clinical evidence profile: real time CGM versus SMBG

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Adults - Real-time CGM	Control	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (%) - Follow up ≤6 months (follow-up ≤6 months; measured with: Battelino, Deiss, Hirsch, Little, O'Connell, Raccah, Radermecker, Tamborlane 2008 (age 25+ years), Tamborlane 2008 (age 15-24 yrs); Better indicated by lower values)												
9	Randomised trials	Serious[a]	Serious[b]	No serious indirectness	Serious[c]	None	451	288	-	MD 0.30 lower (0.46 to 0.14 lower)	VERY LOW	CRITICAL

HbA1c (%) - Follow up ≤6 months (follow-up ≤6 months; measured with: Sequeira; Better indicated by lower values)												
1	Randomised trials	Very serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	39	39	-	8.3% in both groups (at end of first cross-over period)	VERY LOW	CRITICAL
Hypoglycaemia (episodes/day) - Follow up ≤6 months (follow-up ≤6 months; measured with: Raccah, Rademecker; Better indicated by lower values)												
2	Randomised trials	Serious[a]	Serious[f]	No serious indirectness	Serious[g]	None	55	63	-	MD 0.15 higher (0.1 lower to 0.4 higher)	VERY LOW	CRITICAL
Severe hypoglycaemia - Per 100 patient years (follow-up 6 months; measured with: Battelino; Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[h]	None	0	-	-	MD 2.87 higher (3.79 lower to 9.53 higher)	LOW	CRITICAL
Severe hypoglycaemia (no. of patients) - Follow up ≤6 months measured with: Garg, O'Connell, Tamborlane >25 years; (follow-up ≤ 6 months)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[i]	None	5/130 (3.8%)	6/121 (5%)	RR 0.76 (0.25 to 2.27)	12 fewer per 1000 (from 37 fewer to 63 more)	VERY LOW	CRITICAL
Severe hypoglycaemia (annualised rate: patient-year) (follow-up 6 months; measured with: Little 2014; Better indicated by lower values)												
1	Randomised trials	Very serious[j]	No serious inconsistency	No serious indirectness	Very serious[k]	None	48	48	-	MD 0.10 lower (0.88 lower to 0.68 higher)	VERY LOW	CRITICAL
Quality of life: SF12 (scale 0-100) - Physical health - Follow up >6 months (follow-up ≤6 months; measured with: Beck JDRF; Better indicated by higher values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[l]	None	120	106	-	MD 1.4 higher (0.18 lower to 2.98 higher)	MODERATE	IMPORTANT
Quality of life: SF12 (scale 0-100) - Mental health - Follow up >6 months (follow-up ≤6 months; measured with: Beck JDRF; Better indicated by higher values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[m]	None	120	106	-	MD 0.3 lower (2.87 lower to 2.27 higher)	MODERATE	IMPORTANT
Quality of life: SF12 (scale 0-100) - Hypoglycaemia Fear Survey >6 months (follow-up ≤ 6 months; measured with: Beck JDRF; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[n]	None	120	106	-	MD 2.7 lower (6.01 lower to 0.61 higher)	MODERATE	IMPORTANT

Quality of life: SF12 (scale 0-100) - Problem Areas In Diabetes >6 months (follow-up ≤6 months; measured with: Beck JDRF; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[o]	None	120	106	-	MD 0.1 lower (3.85 lower to 3.65 higher)	MODERATE	IMPORTANT
Quality of life total score (scale 0-100 - Follow up ≤6 months (follow-up ≤6 months; measured with: Radermecker; Better indicated by higher values)												
1	Randomised trials	Serious1	No serious inconsistency	No serious indirectness	Serious[p]	None	9	9	-	MD 3 lower (7.38 lower to 1.38 higher)	LOW	IMPORTANT
Adverse events (follow-up ≤6 months; assessed with: Raccah, Little)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[q]	None	3/103 (2.9%)	10/108 (9.3%)	RR 0.36 (0.11 to 1.15)	59 fewer per 1000 (from 82 fewer to 14 more)	VERY LOW	IMPORTANT

(a) Unclear allocation concealment
(b) Heterogeneity = 70%
(c) 95% CI crosses lower MID = 0.35 (0.5 x SD of 0.7).
(d) Unclear allocation concealment; high drop-out rate
(e) Not enough data provided to calculate MD and SD
(f) Heterogeneity = 56%
(g) MID = Median SD across control group multiplied by 0.5 (8.35). Confidence Interval crosses one end of MID.
(h) Confidence interval crosses both default MIDs
(i) Confidence interval crosses both default MIDs (0.75 and 1.25)
(j) Allocation concealment and >10% differential in drop-outs between the two arms
(k) 95% CI crosses both MIDs. MID = 0.6 (0.5 x SD of 1.2)
(l) MID = Median SD of the control group multiplied by 0.5 (3.45)
(m) MID = Median SD of the control group multiplied by 0.5 (4.8)
(n) MID = Median SD of the control group multiplied by 0.5 (6.8)
(o) MID = Median SD of the control group multiplied by 0.5 (7.3)
(p) MID = Median SD of the control group multiplied by 0.5 (2.05). Confidence Interval crosses one end of MID.
(q) 95% CI crosses lower default MID (0.75)

I.4 Insulin therapy

I.4.1 Long-acting insulin

Table 25: Clinical evidence profile: Degludec versus glargine (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Degludec	Glargine	Relative (95% CI)	Absolute	Quality	Importance
Decrease in HbA1c - ≤6 months (Better indicated by lower values); Birkeland x 2 different doses of degludec												
2	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	119	118	-	MD 0.06 lower (0.25 lower to 0.12 higher)	MODERATE	CRITICAL
Decrease in HbA1c - >6 months (Better indicated by lower values); Heller 2012												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	472	157	-	MD 0.01 lower (0.14 to 0.16 higher)	MODERATE	CRITICAL
Body weight change - ≤6 months (Better indicated by lower values); Birkeland x 2 different doses of degludec												
1	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	119	118	-	MD 0.12 lower (0.67 lower to 0.43 higher)	LOW	IMPORTANT
Body weight change - >6 months (Better indicated by lower values); Heller 2012												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	472	157	-	MD 0.2 higher (0.51 lower to 0.91 higher)	MODERATE	CRITICAL
Severe hypoglycaemia (no. Of people) - > 6 months; Heller 2012												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	58/472 (12.3%)	16/157 (10.2%)	RR 1.21 (0.71 to 2.03)	21 more per 1000 (from 30 fewer to 105 more)	LOW	CRITICAL
SF36 Physical component score - ≤6 months (Better indicated by lower values); Home 2012												
1	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	59	59	-	MD 0.67 higher (2.31 lower to 3.65 higher)	MODERATE	IMPORTANT
SF36 Mental component score - ≤6 months (Better indicated by lower values); Home 2012												
1	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	59	59	-	MD 3.01 higher (0.31 to 5.71 higher)	MODERATE	IMPORTANT

(a) Randomisation unclear
(b) Not blinded
(c) Confidence interval compatible with two clinical decisions: benefit of glargine, or no benefit/harm
(d) Confidence interval crosses one MID (is compatible with two clinical decisions: benefit of degludec, or no harm/benefit)

Table 26: Clinical evidence profile: Detemir versus glargine (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Detemir	Glargine	Relative (95% CI)	Absolute		
Decrease in HbA1c - ≤6 months (Better indicated by lower values) ; Renard 2011; Heller 2009												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	317	178	MD 0.00 higher (0.12 lower to 0.13 higher)		MODERATE	CRITICAL
Severe symptomatic hypoglycaemia (number of patients) - ≤6 months; Renard 2011												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[b]	None	4/88 (4.5%)	10/88 (11.4%)	RR 0.4 (0.13 to 1.23)	68 fewer per 1000 (from 99 fewer to 26 more)	LOW	CRITICAL
Major hypoglycaemic episodes/patient-year- >6 months; Heller 2009												
1	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	53.6	57.3	RR 0.94, 95% CI 0.74 to 1.18	-	LOW	CRITICAL
Body weight change- ≤6 months; Renard 2011												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	-0.2kg	0.0	-		VERY LOW	IMPORTANT
Body weight change- >6 months; Heller 2009												
1	Randomised trials	Serious[a,b]	No serious inconsistency	No serious indirectness	Very serious imprecision[d]	None	+0.36kg	+0.42kg	Mean difference -0.06, 95% CI -0.84 to +0.73		VERY LOW	IMPORTANT
Injection site reactions (number of patients) - >6 months; Heller 2009												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/300 (8%)	2/147 (1.4%)	5.88 (1.41 to 24.54)	66 more per 1000 (from 6 more to 320 more)	MODERATE	IMPORTANT

(a) Randomisation unclear, not blinded
(b) Confidence interval compatible with two clinical decisions: benefit of detemir, or no benefit/harm
(c) Confidence interval compatible with three clinical decisions: benefit of detemir, benefit of glargine, or no benefit/harm
(d) Confidence interval crosses both MIDs (is compatible with three clinical decisions: benefit of detemir, benefit of glargine, or no harm/benefit)
(e) Randomisation unclear, allocation concealment unclear, not blinded, no ITT analysis.
(f) SD not given therefore unable to calculate MD and 95% CI

(g) Confidence interval crosses one MID (is compatible with two clinical decisions: benefit of glargine, or no harm/benefit)

Table 27: Clinical evidence profile: Detemir versus NPH (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Detemir	NPH	Relative (95% CI)	Absolute		
HbA1c - ≤6 months (Better indicated by lower values); Golen, Hermanssen, Home 2004, Kolendorf, Pieber 2005, Russell-Jones, Vague, Zachariah												
8	Randomised trials	Very serious1	No serious inconsistency	No serious indirectness	No serious imprecision	None	1515	1131	-	MD 0.09 lower (0.16 to 0.02 lower)	LOW	CRITICAL
HbA1c, change from baseline - ≤6 months; Hermanssen												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	-0.5%	-0.28%	-	-	VERY LOW	CRITICAL
HbA1c, change from baseline - ≤6 months; Kolendorf												
1	Randomised trials	Serious[f]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	-0.3%	-0.3%	No difference	-	LOW	CRITICAL
HbA1c - >6 months (Better indicated by lower values); Bartley, Leeuw, Standl												
3	Randomised trials	Very serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	690	393	-	MD 0.08 lower (0.22 lower to 0.05 higher)	VERY LOW	CRITICAL
HbA1c, change from baseline - >6 months; Leeuw												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	-0.64%	-0.56%	-	-	VERY LOW	CRITICAL
Change in weight - ≤6 months (Better indicated by lower values); Golen, Hermanssen, Home 2004, Russell-Jones, Zachariah												
5	Randomised trials	Very serious[a]	Serious[b]	No serious indirectness	No serious imprecision	None	978	735	-	MD 0.84 lower (1.10 to 0.58lower)	VERY LOW	IMPORTANT
Change in body weight, kg - ≤6 months; Kolendorf												
1	Randomised	Serious[f]	No serious	No serious	Serious	None	-0.3 vs. +1.0 (period 1)			-	LOW	IMPORTANT

	trials		inconsistency	indirectness	imprecision[e]		-0.2 vs. +1.3 (period 2)					
Change in body weight, kg - >6 months; Bartley												
1	Randomised trials	Serious[f]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	+1.7	+2.7	-	-	LOW	IMPORTANT
Change in body weight, kg- >6 months; Leeuw												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	-0.1	+1.2	-	-	VERY LOW	IMPORTANT
Change in body weight, kg - >6 months; Standl												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	None	-0.3	+1.4	-	-	VERY LOW	IMPORTANT
Major hypoglycaemia (no. of patients) - ≤6 months; Hermanssen 2001, Hernansen 2004, Home 2004, Pieber 2005, Russell-Jones, Vague, Zachariah												
7	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[c]	None	94/1424 (6.6%)	77/968 (8.0%)	RR 0.78 (0.58 to 1.04)	18 fewer per 1000 (from 33 fewer to 3more)	VERY LOW	CRITICAL
Major hypoglycaemia (episodes) - ≤6 months; Hermanssen 2001												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	None	4	11	-	-	VERY LOW	CRITICAL
Severe hypoglycaemia, episodes - ≤6 months; Kolendorf												
1	Randomised trials	Serious[f]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	None	19	33	-	-	LOW	CRITICAL
Major hypoglycaemia - >6 months; Bartley, Leeuw, Standl												
3	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	97/701 (13.8%)	77/398 (19.3%)	RR 0.68 (0.52 to 0.89)	62 fewer per 1000 (from 21 fewer to 93 fewer)	LOW	CRITICAL
Injection site reactions - >6 months; Leeuw, Standl												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	5/370 (1.4%)	1/234 (0.4%)	RR 2.06 (0.34 to 12.36)	5 more per 1000 (from 3 fewer to 49 more)	VERY LOW	IMPORTANT

(a) Randomisation/allocation concealment unclear, not blinded
(b) Heterogeneity 53%
(c) Confidence interval compatible with two clinical decisions: benefit of detemir, or no benefit/harm

(d) Confidence interval compatible with three clinical decisions: benefit of detemir, benefit of NPH, or no benefit/harm
(e) SD not given therefore unable to calculate MD and 95% CI
(f) Randomisation unclear, not blinded
(g) Number of episodes rather than patients, thus not put in the meta-analysis

Table 28: Clinical evidence profile: Glargine versus NPH (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Glargine**	**NPH**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c - ≤6 months (Better indicated by lower values); Bolli, Home 2005, Pieber, Raskin, Ratner, Rosenstock, Rossetti												
7	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	1106	1129	-	MD 0.09 lower (0.15 to 0.03 lower)	LOW	CRITICAL
HbA1c, final value, %- ≤6 months; Chatterjee												
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious imprecision[g]	None	8.07	8.26	MD -0.19, 95% CI -0.36 to +0.01	-	LOW	CRITICAL
HbA1c - >6 months (measured with: Porcelatti ; Better indicated by lower values); Porcellatti												
1	Randomised trials	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	61	60	-	MD 0.40 lower (0.44 to 0.36 lower)	HIGH	CRITICAL
HbA1c, change from baseline, % - >6 months; Fulcher												
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious imprecision[j]	None	-0.89	-0.67	-	-	VERY LOW	CRITICAL
Severe hypoglycaemia - ≤6 months; Chatterjee, Home 2005, Pieber, Raskin, Ratner, Rosenstock, Rossetti												
7	Randomised trials	Very serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	65/1094 (5.9%)	125/1100 (11.4%)	RR 0.52 (0.39 to 0.69)	55 fewer per 1000 (from 35 fewer to 69 fewer)	VERY LOW	CRITICAL

Serious hypoglycaemia, episodes/patient/month - ≤6 months; Bolli											
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious imprecision[j]	None	1.01 (1.07)	0.88 (1.04)	-	-	VERY LOW	CRITICAL
Severe hypoglycaemia - >6 months; Porcellatti											
1	Randomised trials	No serious risk of bias	No serious inconsistency 3	No serious indirectness	No serious imprecision	None	0/61 (0%)	0/60 (0%)	-	-	HIGH	CRITICAL
Severe hypoglycaemia, events/100 patient days - >6 months; Fulcher											
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious imprecision[j]	None	0.87	0.99	-	-	VERY LOW	CRITICAL
Change in body weight, kg - ≤6 months; Raskin											
1	Randomised trials	Very serious[l]	No serious inconsistency	No serious indirectness	Serious imprecision[j]	None	+0.12	+0.54	-	-	VERY LOW	IMPORTANT
Change in body weight, kg - >6 months; Fulcher											
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious imprecision[j]	None	+1.97	+2.34	-	-	VERY LOW	IMPORTANT
Change in body weight, kg - >6 months; Porcelatti											
1	Randomised trials	No serious	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	There was no weight change with either treatment				MODERATE	IMPORTANT
Qol, WED: impact, satisfaction, general worries and diabetes-related worries - ≤6 months; Bolli											
1	Randomised trials	Very serious[i]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	NS difference between the groups except diabetes-related worries was SS better in the glargine group				VERY LOW	IMPORTANT
Qol, DTSQ - ≤6 months; Chatterjee											
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	NS difference between groups for hyper or hypo glycaemia. Greater satisfaction with glargine (4 points).				LOW	IMPORTANT
Addqol - ≤6 months; Chatterjee											
1	Randomised trials	Serious[h]	No serious inconsistency	No serious indirectness	Serious imprecision[k]	None	NS difference between the groups, p=0.08				LOW	IMPORTANT
Injection site reactions - ≤6 months; Home 2005, Pieber, Ratner											
3	Randomised	Very	No serious	No serious	Serious[d]	None	46/666	37/6	RR 1.27	15 more per 1000	VERY LOW	IMPORTANT

	trials	serious1	inconsistency	indirectness			(6.9%)	73 (5.5 %)	(0.84 to 1.91)	(from 9 fewer to 50 more)		
Injection site reactions - >6 months; Fulcher												
1	Randomised trials	Very serious[a,e]	No serious inconsistency	No serious indirectness	Very serious[f]	None	5/65 (7.7%)	7/63 (11. 1%)	RR 0.69 (0.23 to 2.07)	34 fewer per 1000 (from 86 fewer to 119 more)	VERY LOW	IMPORTANT
Injection site pain - ≤6 months; Raskin, Ratner												
2	Randomised trials	Very serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	29/574 (5.1%)	4/57 9 (0.7 %)	RR 7.33 (2.58 to 20.79)	44 more per 1000 (from 11 more to 137 more)	VERY LOW	IMPORTANT

(a) Randomisation/allocation concealment unclear; not blinded
(b) Not blinded - but not possible with NPH
(c) Heterogeneity –moderate: I2 >50% but <75%
(d) Confidence interval compatible with benefit of NPH, or no benefit/harm
(e) Drop-out >20% and difference between groups
(f) Confidence interval compatible with three clinical decisions: benefit of glargine, benefit of NPH, or no benefit/harm
(g) CI crosses one MID
(h) Randomisation unclear
(i) Randomisation unclear, allocation concealment unclear, blinding not possible, not true ITT analysis.
(j) SD not given therefore unable to calculate MD and 95% CI
(k) Not enough data given in the study to calculate the RR and 95% CI.
(l) Randomisation unclear, allocation concealment unclear, blinding not possible.

Table 29: Clinical evidence profile: Degludec versus detemir (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Degludec	Detemir	Relative (95% CI)	Absolute	Quality	Importance
Severe hypoglycaemia - no. of patients (≤6 months) (assessed with: Iwamoto 2013)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/33 (0%)	0/32 (0%)	-	-	MODERATE	CRITICAL
Adverse events (≤6 months) (assessed with: Iwamoto 2013)												
1	Randomised	Serious[a]	No serious	No serious	No serious	None	0/33	0/32	-	-	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Degludec	Detemir	Relative (95% CI)	Absolute	Quality	Importance
	trials		inconsistency	indirectness	imprecision		(0%)	(0%)				
Serious adverse events (≤6 months) (assessed with: Iwamoto 2013)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/33 (0%)	0/32 (0%)	-	-	MODERATE	IMPORTANT

(a) Unclear randomisation, no blinding.

Table 30: Clinical evidence profile: Once daily basal insulin versus twice daily basal insulin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Once daily basal insulin	Twice daily basal insulin	Relative (95% CI)	Absolute	Quality	Importance
Hba1c - follow-up ≤6 months; Better indicated by lower values)												
1 Floch 2009	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	250	262	-	MD 0.12 higher (0.01 lower to 0.25 higher)	High	Critical
Hypoglycaemia - Events per patient per day - (follow-up ≤6 months; Better indicated by lower values)												
1 Floch 2009	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	250	262	-	MD 0.21 lower (0.46 lower to 0.04 higher)	High	Critical

I.4.2 Rapid-acting insulin

Table 31: Clinical evidence profile: Lispro versus human insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Lispro	Human	Relative (95% CI)	Absolute	Quality	Importance
HbA1c % (final value) - ≤6 months basal once a day (better indicated by lower values);Annuzzi 2001, Ciofetta 1999, Gale 2000, Heller 1999, Holleman 1997												
5	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.03 lower (0.16 lower to 0.10 higher)	LOW	CRITICAL
HbA1c % (final value) - ≤6 months basal twice a day (better indicated by lower values); Vignati 1997												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[d]	None	0	-	-	MD 0.1 lower (0.31 lower to 0.11 higher)	LOW	CRITICAL
HbA1c % (final value) - ≤6 months basal mixed or not stated (better indicated by lower values); Anderson 1997, Ferguson 2001, Lilly 1995C, Pfutzner 1996												
4	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	Serious[d]	None	0	-	-	MD 0.05lower (0.08 to 0.02 lower)	VERY LOW	CRITICAL
HbA1c % (final value) - ≤6 months GLULISINE basal insulin (better indicated by lower values); Brunetti												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	395	-	-	MD 0.15 lower (0.31 lower to 0.01 higher)	LOW	CRITICAL
HbA1c % (final value) - >6 months basal once a day (better indicated by lower values); Lilly 1995B												
1	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	Very serious[e]	None	0	-	-	MD 0.07 lower (0.98 lower to 0.84 higher)	VERY LOW	CRITICAL
HbA1c % (final value) - >6 months basal mixed or not stated (better indicated by lower values); Lalli, Lilly 1994, Lilly 1995A												
3	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.33 lower (0.47 to 0.2 lower)	LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) ALL STUDIES (≤6 months and >6 months); Ciofetta, Gale, Heller 1999, Andserson, Ferguson												
5	Randomised	Very	No serious	No serious	No serious	None	46/11	74/1122	RR 0.69	2 fewer per 1000	LOW	CRITICAL

	trials	serious[a, b,c]	inconsistency	indirectness	imprecision		237 (0.41 %)	5 (0.66%)	(0.49 to 0.98)	(from 0 fewer to 3 fewer)		
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal once a day; Ciofetta, Gale, Heller 1999,												
3	Randomised trials	Very serious[a, b,c]	Serious6	No serious indirectness	Serious[d]	None	4/168 (23.8 %)	20/156 (12.8%)	RR 0.33 (0.11 to 0.99)	86 fewer per 1000 (from 1 to 114 fewer)	VERY LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated; Anderson, Ferguson												
2	Randomised trials	Very serious[a, b]	No serious inconsistency	No serious indirectness	Serious[d]	None	42/11 041 (0.4%)	54/1104 1 (0.5%)	RR 0.78 (0.54 to 1.11)	1 fewer per 1000 (from 2 fewer to 1 more)	VERY LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated; Lalli 1999												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/28 (0%)	0/28 (0%)	not pooled	not pooled	MODERATE	CRITICAL
Severe hypoglycaemia (episodes) - ≤6 months basal once a day (better indicated by lower values); Gale, Holleman												
2	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 9.46 lower (17.81 to 1.11 lower)	LOW	CRITICAL
Severe hypoglycaemia (episodes) - ≤6 months basal mixed or not stated (better indicated by lower values); Ferguson												
1	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	Serious[d]	None	0	-	-	MD 29 lower (61.73 lower to 3.73 higher)	VERY LOW	CRITICAL
Hypoglycaemia/minor hypo (no. of patients) ALL STUDIES (≤6 months and >6 months); Brunetti, Lilly 1994; Lilly 1995A, Lilly 1995B												
4	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	273/3 98 (68.6 %)	267/400 (66.8%)	RR 1.04 (0.95 to 1.14)	27 more per 1000 (from 33 fewer to 93 more)	LOW	IMPORTANT
Hypoglycaemia/minor hypo (no. of patients) - ≤6 months ; Brunetti												
1	Randomised trials	Serious[c]	No serious inconsistency	No serious indirectness	Serious[g]	None	112/2 02 (55.4 %)	98/193 (50.8%)	RR 1.09 (0.91 to 1.32)	46 more per 1000 (from 46 fewer to 162 more)	LOW	IMPORTANT
Hypoglycaemia/minor hypo (no. of patients) - >6 months; Lilly 1994; Lilly 1995A, Lilly 1995B												

3	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	161/196 (82%)	169/207 (81.6%)	RR 1.01 (0.92 to 1.10)	8 more per 1000 (from 65 fewer to 82 more)	LOW	IMPORTANT
Hypoglycaemia (episodes) - ≤6 months (better indicated by lower values); Heller 1999												
1	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 381 lower (741.05 to 20.95 lower)	LOW	IMPORTANT
Hypoglycaemia (episodes) - >6 months (better indicated by lower values); Lalli 1999												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 4.1 lower (5.75 to 2.45 lower)	MODERATE	IMPORTANT
Hypoglycaemia (episodes/month) - ≤6 months; Anderson 1997, Gale 2000, Pfutzner 1996, Vignati 1997												
4	Randomised trials	Very serious[a, b,c]	Very serious8	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.62 lower (0.91 to 0.33 lower)	VERY LOW	IMPORTANT
Hypoglycaemia/mild hypo (episodes/patient/month) - ≤6 months (better indicated by lower values); Brunetti, Ciofetta, Lilly 1995C												
3	Randomised trials	Very serious[a, c]	Very serious8	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.24 lower (0.64 lower to 0.16 higher)	VERY LOW	IMPORTANT
Hypoglycaemia/mild hypo (episodes/patient/month) - >6 months (better indicated by lower values); Lilly 1994, Lilly 1995A, Lilly 1995B												
3	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.19 lower (1.11 lower to 0.724 higher)	LOW	IMPORTANT
Nocturnal hypoglycaemia (episodes) - ≤6 months (better indicated by lower values); Heller 1999, Holleman 1997												
2	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 132.26 lower (187.13 to 77.39 lower)	LOW	IMPORTANT
Nocturnal hypoglycaemia (episodes/month) - ≤6 months (better indicated by lower values); Gale												
1	Randomised trials	Very serious[a, b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 1.1 lower (1.79 to 0.41 lower)	LOW	IMPORTANT
Weight, kg (final value) - ≤6 months (better indicated by lower values); Anuzzi, Heller 1999, Holleman, Lilly 1995C												
4	Randomised trials	Very serious[a,	No serious inconsistency	No serious indirectness	Very serious[e]	None	0	-	-	MD 0.36 lower (2.1 lower to 1.38	VERY LOW	IMPORTANT

		b,c								higher)		
Weight, kg (final value) - >6 months (better indicated by lower values); Lilly 1994, Lilly 1995A, Lilly 1995B												
3	Randomised trials	Very serious[a, c]	Serious[f]	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.09 higher (2.37 lower to 2.55 higher)	VERY LOW	IMPORTANT
Qol - WED score - ≤6 months (better indicated by lower values); Brunetti												
1	Randomised trials	Very serious[a, c]	No serious inconsistency	No serious indirectness	Serious[i]	None	0	-	-	Mean difference 0.0	VERY LOW	IMPORTANT

(a) Randomisation and allocation concealment unclear
(b) Crossover study/studies with no washout period
(c) Unclear if correct ANCOVA analysis done (for crossover studies)
(d) Wide confidence interval consistent with 2 clinical decisions (benefit or no difference)
(e) Wide confidence interval consistent with 3 clinical decisions (benefit, harm or no difference)
(f) Heterogeneity 50% to 74%
(g) Wide confidence interval consistent with 2 clinical decisions (no difference or harm)
(h) Heterogeneity 75% or more
(i) Mean difference 0, SE 0, precision not estimable

Table 32: Clinical evidence profile: Lispro versus Glulisine (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Lispro	Glulisine	Relative (95% CI)	Absolute	Quality	Importance
HbA1c % (final value) - >6 months (better indicated by lower values); Dreyer 2005A, Kawamori												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.01 lower (0.15 lower to 0.13 higher)	MODERATE	CRITICAL
Hypoglycaemia (episodes/patient-month) - >6 months (better indicated by lower values); Kawamori												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.07 higher (0.03 lower to 0.17 higher)	MODERATE	IMPORTANT
Hypoglycaemia (episodes/ patient -months) - >6 months (better indicated by lower values); Dreyer 2005A												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0	-	-	MD 0.16 lower (0.83 lower to 0.51 higher)	VERY LOW	IMPORTANT

Severe hypoglycaemia (episodes/ patient -month) - >6 months (better indicated by lower values); Kawamori											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	0	-	-	Mean difference 0.0	LOW	CRITICAL
Severe hypoglycaemia (episodes/ patient -months) - >6 months (better indicated by lower values); Dreyer 2005A											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.01 lower (0.03 lower to 0.01 higher)	MODERATE	CRITICAL
Nocturnal hypoglycaemia (episodes/ patient -months) - >6 months (better indicated by lower values); Dreyer 2005A											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.02 lower (0.15 lower to 0.11 higher)	MODERATE	IMPORTANT
Injection site reactions (no. of patients) - >6 months; Dreyer 2005A											
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	14/341 (4.1%)	11/342 (3.2%)	RR 1.28 (0.59 to 2.77)	9 more per 1000 (from 13 fewer to 57 more)	VERY LOW	IMPORTANT

(a) Randomisation and allocation concealment unclear
(b) Wide confidence interval consistent with 3 clinical decisions (benefit, harm or no difference)
(c) Mean difference 0, SE 0, precision not estimable

Table 33: Clinical evidence profile: Aspart versus human insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Aspart**	**Human**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c % (final value) - ≤6 months basal once a day (better indicated by lower values); Heller 2004, Nielsen, Raskin 2000A												
3	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.15 lower (0.26 to 0.04 lower)	LOW	CRITICAL
HbA1c % (final value) - ≤6 months basal twice a day (better indicated by lower values); Brock												
1	Randomised trials	Very serious[a,b,c]	No serious inconsistency	No serious indirectness	Serious[d]	None	0	-	-	Mean difference 0.0	VERY LOW	CRITICAL
HbA1c % (final value) - ≤6 months basal mixed or not stated (better indicated by lower values); Home 2000/Bott 2003, Tamas 2001												
2	Randomised trials	Very serious[a,b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.14 lower (0.21 to 0.07	LOW	CRITICAL

										lower)		
HbA1c % (final value) - >6 months basal mixed or not stated (better indicated by lower values); Home 2006												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.16 lower (0.32 lower to 0 higher)	LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) all studies (≤6 months and >6 months)												
3	Randomised trials	Very serious[b,e]	No serious inconsistency	No serious indirectness	Serious[f]	None	288/1487 (19.4%)	140/757 (18.5%)	RR 0.89 (0.74 to 1.07)	20 fewer per 1000 (from 48 fewer to 13 more)	VERY LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated; Home 2000/Bott 2003, Tamas 2001												
2	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	Serious[f]	None	126/920 (13.7%)	82/571 (14.4%)	RR 0.87 (0.67 to 1.12)	19 fewer per 1000 (from 47 fewer to 17 more)	LOW	CRITICAL
Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated; Home 2006												
1	Randomised trials	Very serious[b,e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	162/567 (28.6%)	58/186 (31.2%)	RR 0.92 (0.71 to 1.18)	25 fewer per 1000 (from 90 fewer to 56 more)	LOW	CRITICAL
Hypoglycaemia/minor hypoglycaemia (no. of patients) - ≤6 months; Home 1998, Home 2000/Bott 2003												
2	Randomised trials	Very serious[a,b,c]	Serious[g]	No serious indirectness	No serious imprecision	None	579/811 (71.4%)	294/462 (63.6%)	RR 1.03 (0.96 to 1.11)	19 more per 1000 (from 25 fewer to 70 more)	VERY LOW	IMPORTANT
Hypoglycaemia/minor hypoglycaemia (no. of patients) - >6 months; Home 2006												
1	Randomised trials	Very serious[b,e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	488/567 (86.1%)	153/186 (82.3%)	RR 1.05 (0.97 to 1.13)	41 more per 1000 (from 25 fewer to 107 more)	LOW	IMPORTANT
Hypoglycaemia (episodes/patient/week) - ≤6 months (better indicated by lower values); Brock 2011												
1	Randomised trials	Very serious[a,b,c]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.2 lower (0.3 to 0.1 lower)	LOW	IMPORTANT
QoI - DTSQ (score 0-6) - ≤6 months (better indicated by lower values); Tamas 2001												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.33 lower (0.56 to 0.1 lower)	MODERATE	IMPORTANT

QoI - DTSQ (score 0-36) - ≤6 months (better indicated by lower values); Home 2000/Bott 2003												
1	Randomised trials	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 2.3 higher (1.29 to 3.31 higher)	MODERATE	IMPORTANT

(a) Unclear if correct ANCOVA analysis done (for crossover studies)
(b) Randomisation and allocation concealment unclear
(c) Crossover study/studies with no washout period
(d) Mean difference 0, SE 0, precision not estimable
(e) Drop-outs unacceptable; differential between two arms >10%; due to ineffective therapy in human insulin arm
(f) Wide confidence interval consistent with 2 clinical decisions (benefit or no difference)
(g) Heterogeneity 50% to 74%

Table 34: Clinical evidence profile: Glulisine versus human insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Glulisine**	**Human**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c (change score) - <6 months; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None				MD 0.03 lower (0.13 lower to 0.08 higher)	MODERATE	CRITICAL
Severe/major hypoglycaemia (no. of patients) - <6 months; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	49/582 (8.4%)	56/556 (10.1%)	RR 0.84 (0.58 to 1.2)	16 fewer per 1000 (from 42 fewer to 20 more)	LOW	CRITICAL
Severe hypoglycaemia (episodes/patient/month) - <6 months (better indicated by lower values) ; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.08 lower (0.2 lower to 0.04 higher)	MODERATE	CRITICAL
Hypoglycaemia/minor hypo (no. of patients) - <6 months ; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	486/582 (83.5%)	456/556 (82%)	RR 1.02 (0.97 to 1.07)	16 more per 1000 (from 25 fewer to 57 more)	MODERATE	IMPORTANT
Hypoglycaemia (episodes/patient/month) - <6 months basal (better indicated by lower values) ; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
1	Randomise	Serious[a]	No serious	No serious	Very	None	0	-	-	MD 0.08 higher	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Glulisine	Human	Relative (95% CI)	Absolute		
	d trials		inconsistency	indirectness	serious[c]					(0.41 lower to 0.58 higher)		
Nocturnal hypoglycaemia (no. of patients) - <6 months; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	317/582 (54.5%)	302/556 (54.3%)	RR 1 (0.9 to 1.12)	0 fewer per 1000 (from 54 fewer to 65 more)	MODERATE	IMPORTANT
Nocturnal hypoglycaemia (episodes/patients/month) - <6 months (better indicated by lower values) ; Garg 2005 and Garg 2005 (pre-meal and post-meal data)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.07 lower (0.24 lower to 0.1 higher)	MODERATE	IMPORTANT

(a) Randomisation and allocation concealment unclear
(b) Wide confidence interval consistent with 2 clinical decisions (benefit or no difference)
(c) Wide confidence interval consistent with 3 clinical decisions (benefit, harm or no difference)

I.4.3 Mixed insulin

Table 35: Clinical evidence profile: Mixed insulin (human mix) versus basal-bolus insulin (less than or equal to 6 months)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MIX	BASAL-BOLUS: human insulin mix	Relative (95% CI)	Absolute		
HbA1c - final value (≤6 months) - Mix part of basal-bolus (measured with: Fanelli; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	0	-	-	MD 0.5 higher (0.17 to 0.83 higher)	VERY LOW	CRITICAL
Nocturnal Hypoglyc, episodes/patient-day (≤6 months) - Mix part of basal-bolus (measured with: Fanelli; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.02 higher (0.01 to 0.03	LOW	IMPORTANT

										higher)		
Severe/major Hypoglycaemia, number of patients- Mix part of basal-bolus (≤6 months) (assessed with: Fanelli)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/22 (0%)	0/22 (0%)	not pooled	not pooled	LOW	CRITICAL
Ketoacidosis, number of patients (≤6 months) (assessed with: Kachadurian)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	1/29 (3.4 %)	0/43 (0%)	RR 4.4 (0.19 to 104.42)	-	VERY LOW	IMPORTANT
Injection site reactions, number of patients (≤6 months) (assessed with: Khachadurian)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	2/29 (6.9 %)	3/43 (7%)	RR 0.99 (0.18 to 5.55)	1 fewer per 1000 (from 57 fewer to 317 more)	VERY LOW	IMPORTANT

(a) Unclear randomisation; allocation concealment and blinding not mentioned. No washout period
(b) 95% CI crosses upper MID (MID = 0.2; 0.5 x SD of 0.4)
(c) 95% CI crosses both default MIDs (0.75 and 1.25)

Table 36: Clinical evidence profile: Mixed insulin (lispro mix) versus basal-bolus insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MIX**	**BASAL-BOLUS: Lispro mix**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c - final value (≤6 months) - True mix (twice/day vs basal-bolus) (measured with: Janssen; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	0	-	-	MD 0.5 higher (0.25 to 0.75 higher)	VERY LOW	CRITICAL
HbA1c - final value (≤6 months) - Mix part of basal-bolus (measured with: Ciofetta - lispro, Ciofetta - human, Herz; Better indicated by lower values)												
3	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	0	-	-	MD 0.32 lower (0.54 to 0.11 lower)	VERY LOW	CRITICAL
Hypoglycaemia, episodes/patient (≤6 months) - Mix part of basal-bolus (measured with: Herz; Better indicated by lower values)												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.3 lower (1.67 lower to	LOW	IMPORTANT

										1.07 higher)		
Hypoglycaemia, episodes/patient /month (≤6 months) - Mix part of basal-bolus (measured with: Ciofetta - lispro, Ciofetta - human; Better indicated by lower values)												
2	Randomised trials	Very serious[c]	Very serious6	No serious indirectness	Very serious[g]	None	16	16	-	MD 0.64 lower (2.53 lower to 1.25 higher)	VERY LOW	IMPORTANT
Nocturnal Hypoglyc, number of patients (≤6 months) - Mix part of basal-bolus (assessed with: Herz)												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	69/109 (63.3%)	71/109 (65.1%)	RR 0.97 (0.8 to 1.18)	20 fewer per 1000 (from 130 fewer to 117 more)	LOW	IMPORTANT
Severe/major Hypoglycaemia, number of patients (≤6 months) - True mix (twice/day vs basal-bolus) (assessed with: Janssen)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[h]	None	1/17 (5.9 %)	1/18 (5.6%)	RR 1.06 (0.07 to 15.62)	3 more per 1000 (from 52 fewer to 812 more)	VERY LOW	CRITICAL
Severe/major Hypoglycaemia, number of patients (≤6 months) - Mix part of basal-bolus (assessed with: Ciofetta - lispro, Ciofetta - human, Herz)												
3	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[h]	None	6/69 (8.7 %)	10/72 (13.9%)	RR 0.63 (0.25 to 1.62)	51 fewer per 1000 (from 104 fewer to 86 more)	VERY LOW	CRITICAL
Weight change, kg (≤6 months) - Mix part of basal-bolus (measured with: Herz; Better indicated by lower values)												
1	Randomised trials	Very serious[e]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.7 lower (1.28 to 0.12 lower)	LOW	IMPORTANT

(a) Unclear randomisation and allocation concealment. Open label. ITT analysis.
(b) 95% CI crosses upper MID (MID=0.3; 0.5 x SD of 0.6)
(c) Unclear randomisation and allocation concealment. Open label.
(d) 95% CI crosses lower MID (MID = 0.26; 0.5 x SD of 0.51)
(e) Unclear randomisation and allocation concealment. Open label. No wash-out period between cross-over. ITT analysis,
(f) Significant heterogeneity I2>75%
(g) 95% CI crosses both MIDs (MID = 1.13 that is, 0.5 x SD of 2.26)
(h) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)

Table 37: Clinical evidence profile: Mixed insulin (aspart mix) versus basal-bolus insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MIX	BASAL-BOLUS: Aspart mix	Relative (95% CI)	Absolute	Quality	Importance
Hypoglycaemia, number of patients - Mix part of basal-bolus (≤6 months) (assessed with: Hirsch)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	341/362 (94.2%)	168/180 (93.3%)	RR 1.01 (0.96 to 1.06)	9 more per 1000 (from 37 fewer to 56 more)	LOW	IMPORTANT
Nocturnal Hypoglyc, number of patients - Mix part of basal-bolus (≤6 months) (assessed with: Hirsch)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious2	None	192/362 (53%)	125/180 (69.4%)	RR 0.76 (0.67 to 0.88)	167 fewer per 1000 (from 83 fewer to 229 fewer)	VERY LOW	IMPORTANT
Severe/major Hypoglycaemia, number of patients - Mix part of basal-bolus (≤6 months) (assessed with: Chen, Hirsch)												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious3	None	37/389 (9.5%)	23/207 (11.1%)	RR 0.83 (0.51 to 1.35)	19 fewer per 1000 (from 54 fewer to 39 more)	VERY LOW	CRITICAL
SF-36 Physical (≤6 months) - True mix (twice/day versus basal-bolus) (measured with: Hirsch; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.3 higher (0.65 lower to 1.25 higher)	LOW	IMPORTANT
SF-36 Mental (≤6 months) - True mix (twice/day versus basal-bolus) (measured with: Hirsch; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.1 lower (1.55 lower to 1.35 higher)	LOW	IMPORTANT
Treatment satisfaction, % (≤6 months - Lispro or Aspart) - True mix (twice/day versus basal-bolus) (measured with: Testa; Better indicated by lower values)												
1	Randomised trials	Very serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 27.7 lower (39.22 to 16.18 lower)	LOW	IMPORTANT
Regimen acceptance, % (≤6 months) - Lispro or Aspart - True mix (twice/day versus basal-bolus) (measured with: Testa; Better indicated by lower values)												
1	Randomised	Very	No serious	No serious	Serious5	None	0	-	-	MD 4 lower (7.55	VERY	IMPORTANT

	trials	serious[d]	inconsistency	indirectness						to 0.45 lower)	LOW	

(a) Unclear randomisation and allocation concealment. Open label.
(b) 95% CI crosses one default MID (0.75)
(c) 95% CI crosses both MIDs (0.75 and 1.25)
(d) Unclear randomisation and allocation concealment. Open label. No wash-out period between cross-over. ITT analysis,
(e) 95% CI crosses lower MID (MID=1.35; 0.5 x SD of 2.7)

Table 38: Clinical evidence profile: Mixed insulin versus mixed insulin (less than or equal to 6 months and more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MIX**	**MIX**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
HbA1c, final value (≤6 months) (measured with: Dunbar, Roach 2004; Better indicated by lower values)												
2	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	64	64	-	MD 0.09 lower (0.33 lower to 0.15 higher)	LOW	CRITICAL
Nocturnal Hypoglycaemia, episodes/patient (≤6 months) (measured with: Roach 1999; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	37	37	-	MD 1.40 lower (3.16 lower to 0.36 higher)	VERY LOW	IMPORTANT
Severe/major Hypoglycaemia, number of patients (≤6 months) (assessed with: Cucinotta, Dunbar, Roach)												
3	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	9/136 (6.6%)	8/136 (5.9%)	RR 1.12 (0.46 to 2.75)	7 more per 1000 (from 32 fewer to 103 more)	VERY LOW	CRITICAL

(a) Unclear randomisation and allocation concealment. Open label. No wash-out period between cross-over. ITT analysis.
(b) 95% CI crosses one default MID (MID=0.5 x SD of 5.1 that is, 2.55)
(c) 95% CI crosses both default MIDs (0.75 and 1.25)

I.4.4 Adjuncts (Metformin, GLP-1 agonists and amylin analogues)

Table 39: Clinical evidence profile: Pramlintide with Insulin versus insulin

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pramlintide plus insulin versus insulin alone	Control	Relative (95% CI)	Absolute		
HbA1c (%) ≤ 6months (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	14	14	-	MD 0.3 lower (0.87 lower to 0.27 higher)	LOW	CRITICAL
HbA1c (%) >6 months (Better indicated by lower values)												
3	Randomised trials	Serious[a]	Serious[c]	No serious indirectness	No serious imprecision	None	647	469	-	MD 0.26 lower (0.34 to 0.18 lower)	LOW	
Severe hypoglycaemia ≤6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	3/173 (1.7%)	1/42 (2.4%)	RR 0.73 (0.08 to 6.83)	6 fewer per 1000 (from 22 fewer to 139 more)	VERY LOW	
Hypoglycaemia ≤6months												
2	Randomised trials	Serious[a]	Serious[e]	No serious indirectness	Serious[f]	None	114/140 (81.4%)	41/56 (73.2%)	RR 1.08 (0.91 to 1.27)	59 more per 1000 (from 66 fewer to 198 more)	VERY LOW	
Hypoglycaemia >6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	136/148 (91.9%)	134/147 (91.2%)	RR 1.01 (0.94 to 1.08)	9 more per 1000 (from 55 fewer to 73 more)	LOW	
Weight change ≤6 months (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[g]	None	14	14	-	MD 1 lower (2.18 lower to 0.18 higher)	LOW	
Weight change >6 months (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	148	147	-	MD 2.5 lower (3.26 to 1.74 lower)	MODERATE	
Adverse event combined outcome gastrointestinal side-effects ≤ 6 months												

1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	21/41 (51.2%)	4/22 (18.2%)	RR 2.82 (1.11 to 7.18)	331 more per 1000 (from 20 more to 1000 more)	LOW	
Adverse event nausea ≤6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/126 (21.4%)	1/42 (2.4%)	RR 9 (1.26 to 64.22)	190 more per 1000 (from 6 more to 1000 more)	MODERATE	
Adverse event nausea >6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	93/148 (62%)	53/147 (36%)	RR 1.75 (1.36 to 2.3)	190 more per 1000 (from 6 more to 1000 more)	MODERATE	
Adverse event vomiting >6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	20/148 (13.5%)	9/147 (6.1%)	RR 2.21 (1.04 to 4.69)	74 more per 1000 (from 2 more to 226 more)	LOW	
Adverse event anorexia ≤6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	5/126 (4%)	0/42 (0%)	RR 3.72 (0.21 to 65.97)	-	LOW	
Adverse event anorexia >6 months												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/142 (9.2%)	3/147 (2%)	RR 4.49 (1.31 to 15.41)	71 more per 1000 (from 6 more to 294 more)	MODERATE	

(a) Unclear randomisation, no information on allocation concealment
(b) Confidence interval crosses one end of MID (MID = Median SD across the control groups multiplied by 0.5 [0.395])
(c) Heterogeneity: I2=75% unable to explain with subgroup analysis as all three studies in same pre-specified subgroups
(d) Confidence interval crosses both ends of default MID (0.75 and 1.25)
(e) Heterogeneity: I2=53%
(f) Confidence interval crosses one end of default MID (0.75 and 1.25)
(g) Confidence interval crosses one end of MID (MID = media across the control groups multiplied by 0.5 [1.1])

Table 40: Clinical evidence profile: Metformin in combination with insulin versus insulin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Metformin plus insulin versus insulin alone	Control	Relative (95% CI)	Absolute		
HbA1c (%) ≤6 months (measured with: Burchardt, Jacobsen, Khan, Meyer; Better indicated by lower values)												
4	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	79	78	-	MD 0.17 lower (0.44 lower to 0.1 higher)	LOW	CRITICAL
HbA1c (%) ≤6 months - single study (measured with: Pitocco; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	21	21	-	MD 0.17 higher (0.36 lower to 0.72 higher)	LOW	CRITICAL
HbA1c (%) >6 months (measured with: Lund; Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	None	48	50	-	MD 0.13 higher (0.18 lower to 0.44 higher)	MODERATE	CRITICAL
Severe hypoglycaemia ≤6 months (assessed with: Meyer)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	3/31 (9.7%)	5/31 (16.1%)	RR 0.6 (0.16 to 2.3)	65 fewer per 1000 (from 135 fewer to 210 more)	LOW	CRITICAL
Severe hypoglycaemia episodes ≤6 months - single study (measured with: Pitocco; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	21	21	-	MD 0 higher (0 to 0 higher)	MODERATE	CRITICAL
Severe hypoglycaemia >6 months (assessed with: Lund)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[d]	None	15/49 (30.6%)	10/50 (20%)	RR 1.53 (0.76 to 3.07)	106 more per 1000 (from 48 fewer to 414 more)	MODERATE	CRITICAL

Hypoglycaemia >6 months (assessed with: Lund)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	48/49 (98%)	49/50 (98%)	RR 1 (0.94 to 1.06)	0 fewer per 1000 (from 59 fewer to 59 more)	HIGH	IMPORTANT
Dose of insulin ≤6 months (measured with: Jacobsen, Khan, Meyer; Better indicated by lower values)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	58	58	-	MD 4.99 lower (8.35 to 1.63 lower)	LOW	IMPORTANT
Dose of insulin ≤6 months - single study (measured with: Pitocco; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	21	21	-	MD 0.027 lower (0.10 lower to 0.51 higher)	LOW	IMPORTANT
Dose of Insulin >6 months (Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	48	50	-	MD 5.7 lower (8.49 to 2.91 lower)	LOW	IMPORTANT
Weight change ≤6 months (measured with: Jacobsen, Khan; Better indicated by lower values)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	27	27	-	MD 3.71 lower (5.76 to 1.66 lower)	MODERATE	IMPORTANT
Weight change ≤6 months - single study (measured with: Pitocco; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	21	21	-	MD 2.27 lower (3.99 to 0.54 lower)	MODERATE	IMPORTANT
Weight change >6 months (measured with: Lund; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[g]	None	48	50	-	MD 1.74 lower (3.31 to 0.17 lower)	LOW	IMPORTANT
Adverse event gastrointestinal discomfort ≤6 months (assessed with: Jacobsen, Khan, Meyer)												
3	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	13/58 (22.4%)	3/57 (5.3%)	RR 3.81 (1.24 to 11.65)	148 more per 1000 (from 13 more to 561 more)	LOW	IMPORTANT

Adverse event vomiting ≤6 months (assessed with: Jacobsen)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[h]	None	1/12 (8.3%)	0/11 (0%)	RR 2.77 (0.12 to 61.65)	-	VERY LOW	IMPORTANT

(a) Unclear randomisation, no information on allocation concealment
(b) 95% CI crosses lower end of MID (MID = 0.4; 0.5 x SD of 0.8)
(c) 95% CI crosses upper end of MID (MID = 0.36; 0.5 x SD of 0.72)
(d) Confidence interval crosses one end of default MID (0.75 and 1.25)
(e) Confidence interval crosses one end of MID (MID = Median SD across the control groups multiplied by 0.5 (3.52))
(f) 95% CI crosses upper MID (MID = 25; 0.5 x SD of 0.49)
(g) Confidence interval crosses one end of MID (MID= Median SD across the control groups multiplied by 0.5 (1.1))
(h) Confidence interval crosses both ends of default MID (0.75 and 1.25)

Table 41: Clinical evidence profile: Liraglutide with insulin versus insulin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Liraglutide plus insulin versus insulin alone	Control	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (%) ≤6 months (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	9	10	-	MD 0.27 lower (0.62 lower to 0.08 higher)	MODERATE	
Dose of Insulin ≤6 months (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	9	10	-	MD 0.15 lower (0.23 to 0.06 lower)	HIGH	
Weight change ≤6 months (better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[b]	None	9	10	-	MD 2 lower (3.32 to 0.68 lower)	MODERATE	

(a) Confidence interval crosses one end of MID (MID = Median SD across the control groups multiplied by 0.5 [0.39])
(b) Confidence interval crosses one end of MID (MID= Median SD across the control groups multiplied by 0.5 [1.1])

Table 42: Clinical evidence profile: Exenatide with insulin versus insulin

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Exenatide plus insulin	Insulin alone	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (%) ≤6 months (measured with: Sarkar; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	Very serious[c,d]	None	13	13	-	MD 0.10 lower (0.52 lower to 0.32 higher)	VERY LOW	

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Exenatide plus insulin	Insulin alone	Relative (95% CI)	Absolute		
Dose of Insulin ≤6 months (measured with: Sarkar; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious[b]	Serious[e]	None	13	13	-	MD 0.07 lower (0.16 lower to 0.02 higher)	VERY LOW	
Weight change ≤6 months (measured with: Sarkar; Better indicated by lower values)												
1	Randomised trials	Very serious[b]	No serious inconsistency	Serious[b]	Serious[f,g]	None	13	13	-	MD 4.20 lower (13.08 lower to 4.68 higher)	VERY LOW	

(a) Unclear allocation concealment, open label, no washout period, approximately 10% difference between arms for drop-outs.
(b) Some patients on exenatide had additional daclizumab (% not reported), although study did an analysis to show this had no effect.
(c) Confidence interval crosses one end of MID (MID = Median SD across the control groups multiplied by 0.5 [0.395])
(d) 95% CI crosses both MIDs (MID = 0.35; 0.5xSD of 0.7)
(e) 95% CI crosses the lower MID (MID=0.065; 0.5 x SD of 0.13)
(f) Confidence interval crosses one end of MID (MID= Median SD across the control groups multiplied by 0.5 [1.1])
(g) 95% CI crosses lower MID (MID=5.5; 0.5 x SD of 11.0)

I.4.5 Needle, length, site and rotation

Table 43: Clinical evidence profile: Insulin delivery (needle length) - 4 mm x 32G PN versus 5 mm x 31G PN

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	4mm x 32G PN	5mm x 31G PN	Relative (95% CI)	Absolute		
Hypoglycaemia - 4 mm versus 5 mm - Follow up ≤6 months												
1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	Very serious[c]	None	36/173 (20.8%)	21/89 (23.6%)	RR 0.88 (0.55 to 1.42)	28 fewer per 1000 (from 106 fewer to 99 more)	VERY LOW	CRITICAL
Injection site pain - 4mm versus 5mm - Follow up ≤6 months												

1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	Very serious[c]	None	27/173 (15.6%)	11/89 (12.4%)	RR 1.26 (0.66 to 2.43)	32 more per 1000 (from 42 fewer to 177 more)	VERY LOW	IMPORTANT
Pain scores - 4mm versus 5mm - Follow up ≤6 months (measured with: Visual Analogue Scale; Better indicated by lower values)												
1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	No serious imprecision	None	68	68	-	11.91 lower (22.91 lower to 0.91 lower)	LOW	IMPORTANT

(a) Allocation concealment not reported
(b) Data from mixed population with 37% type 1 diabetes and no sub-group analysis
(c) Confidence interval crosses both ends of default MID (0.75; 1.25).

Table 44: Clinical evidence profile: Insulin delivery (needle length) - 4 mm x 32G PN versus 8 mm x 31G PN

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**4mm x 32G PN**	**5mm x 31G PN**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Hypoglycaemia - 4 mm versus 5 mm - Follow up ≤6 months												
1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	Very serious[c]	None	36/173 (20.8%)	21/89 (23.6%)	RR 0.88 (0.55 to 1.42)	28 fewer per 1000 (from 106 fewer to 99 more)	VERY LOW	CRITICAL
Injection site pain - 4mm versus 5mm - Follow up ≤6 months												
1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	Very serious[c]	None	27/173 (15.6%)	11/89 (12.4%)	RR 1.26 (0.66 to 2.43)	32 more per 1000 (from 42 fewer to 177 more)	VERY LOW	IMPORTANT
Pain scores - 4mm versus 5mm - Follow up ≤6 months (measured with: Visual Analogue Scale; Better indicated by lower values)												
1 Hirsch 2010	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	No serious imprecision	None	68	68	-	11.91 lower (22.91 lower to 0.91 lower)	LOW	IMPORTANT

(a) Allocation concealment not reported
(b) Data from mixed population with 37% type 1 diabetes and no sub-group analysis
(c) Confidence interval crosses both ends of default MID (0.75; 1.25).

Table 45: Clinical evidence profile: Insulin delivery (needle length) - 4 mm x 32G PN versus 6 mm x 32G PN

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	4 mm x 32G PN	8mm x 31G PN	Relative (95% CI)	Absolute	Quality	Importance
Pain scores - 4mm versus 6mm - Follow up ≤ 6 months (measured with: 150 mm Visual Analogue Scale; Better indicated by lower values)												
1 Miwa 2012	Randomised trials	Serious[a]	No serious inconsistency	Serious indirectness[b]	Serious imprecision[c]	None	38	38	-	16.60 lower (25.95 lower to 7.25 lower)	VERY LOW	IMPORTANT

(a) Allocation concealment not reported
(b) Data from mixed population with 12% type 1 diabetes and no subgroup analysis
(c) Confidence interval crosses one end of default MID (SD multiplied by 0.5).

Table 46: Clinical evidence profile: Insulin delivery (needle length) - 5 mm x 31G PN versus 8 mm x 31G PN

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	5 mm x 31G PN	8mm x 31G PN	Relative (95% CI)	Absolute	Quality	Importance
Hypoglycaemia - 5 mm vs 8 mm - Follow up ≤ 6 months												
1 kreugel 2011	Randomised trials	Very serious[a]	No serious inconsistency	Serious indirectness[b]	No serious imprecision	None	130	130	-	MD 0.12 lower (0.35 lower to 0.11 higher)	VERY LOW	CRITICAL

(a) Allocation concealment not reported, open label, no ITT analysis
(b) Data from mixed population with 5% type 1 diabetes and no separated data reported or subgroup analysis carried out for type 1 diabetes participants.

I.5 Pancreas transplant and islet cell transplantation

None

I.6 Hypoglycaemia

I.6.1 Identification and quantification of impaired awareness of hypoglycaemia

None

I.6.2 Recovering hypoglycaemia awareness

Table 47: Clinical evidence profile: Structured education and hypoglycaemia avoidance versus standard care

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Education and avoidance	Standard care	Relative	Absolute	Quality	Importance
Hypoglycaemia unawareness ≤6months: HAQ (Clarke) (follow-up 6 months; range of scores: 0-7; Better indicated by higher values). Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	74	72	-	MD 0.7 lower (1.3 to 0.1 lower)	VERY LOW	CRITICAL
Hypoglycaemia unawareness ≤6months: Gold Score modified VAS (follow-up 6 months; range of scores: 0-10; Better indicated by higher values). Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	74	72	-	MD 0.8 higher (0.2 to 1.4 higher)	VERY LOW	CRITICAL
Severe hypoglycaemia ≤6months: events/patient-year (follow-up 6 months; Better indicated by lower values). Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	74	72	-	MD 0.3 lower (1 lower to 0.4 higher)	LOW	CRITICAL
Severe hypoglycaemia ≤6months: events/patient/6 months (follow-up 6 months; Better indicated by lower values) **SD not given.** HAATT+ SMBG versus SMBG alone [Cox 2004]												

1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[i]	None	30	30	-	Unable to calculate MD[(i)(j)]	VERY LOW	CRITICAL
Nocturnal hypoglycaemia ≤6months: events/patient/6 months (follow-up 6 months; Better indicated by lower values) **SD not given.** HAATT+ SMBG versus SMBG alone [Cox 2004]												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	Very serious[i]	None	30	30	-	Unable to calculate MD[(i)(k)]	VERY LOW	CRITICAL
HbA1c % (final values) ≤6months (follow-up 6 months; Better indicated by lower values). Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision[f]	None	74	72	-	MD 0.1 higher (0.18 lower to 0.38 higher)	MODERATE	CRITICAL
Quality of Life ≤6months: PAID (follow-up 6 months; range of scores: 0-100; Better indicated by lower values). Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[g]	None	74	72	-	MD 0.7 higher (3.2 lower to 4.6 higher)	VERY LOW	CRITICAL
Quality of Life ≤6months: addqol (follow-up 6 months; range of scores: -3-3; Better indicated by higher values . Hypos versus education alone [Hermanns 2007]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision[h]	None	74	72	-	MD 0.1 lower (0.3 lower to 0.1 higher)	LOW	CRITICAL
Autonomic symptom score during clamp ≤6months (follow-up 2 weeks; measured with: six autonomic symptoms ; range of scores: 0-30; Better indicated by higher values)												
1	Observational study	Very serious[l]	No serious inconsistency	No serious indirectness	Serious[m]	None	16	5	-	MD 5.0 higher (3.0 to 7.0 higher)	VERY LOW	IMPORTANT
Neuroglycopenic symptom score during clamp ≤6months (follow-up 2 weeks; measured with: five neuroglycopenic symptoms ; range of scores: 0-25; Better indicated by higher values)												
1	Observational study	Very serious[l]	No serious inconsistency	No serious indirectness	Serious[m]	None	16	5	-	MD 3.6 higher (1.14 to 6.06 higher)	VERY LOW	IMPORTANT

(a) Information is from one study at very high risk of bias - unclear randomisation, unclear allocation concealment and blinding not mentioned (subjective outcome)
(b) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.3 to -0.1; MID = ±0.5)
(c) 95% CI crosses the upper default MID (95% CI for SMD used as only one study: 0.2 to 1.4; MID = ±0.5)
(d) Information is from one study at high risk of bias - unclear randomisation, unclear allocation concealment and blinding not mentioned (objective outcome)
(e) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.0 to 0.4; MID = ±0.5)
(f) 95% CI does not cross either default MID (95% CI for SMD used as only one study: -0.2 to 0.4; MID = ±0.5)
(g) 95% CI crosses both the default MIDs (95% CI for SMD used as only one study: -3.2 to 4.6; MID = ±0.5)

(h) 95% CI does not cross either default MID (95% CI for SMD used as only one study: -0.3 to 0.1; MID = ±0.5)
(i) SD not given therefore unable to calculate MD and 95% CI
(j) Data given: SE and avoidance 0.4, Control 1.7; p=0.03
(k) Data given: SE and avoidance 0.8, Control 1.6; p=0.06
(l) Information is from one study at very high risk of bias - non-randomised study
(m) 95% CI crosses the upper default MID (95% CI for SMD used as only one study; MID = ±0.5)

Table 48: Clinical evidence profile: Insulin lispro versus regular human insulin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Lispro**	**Human Insulin**	**Relative (95% CI)**	**Absolute**		
Severe Hypoglycaemia ≤6months, number of patients (follow-up 6 months). [Ferguson 2001]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	18/33 (54.5 %)	18/33 54.6%	RR 1 (0.64 to 1.55)	0 fewer per 1000 (from 197 fewer to 300 more)	VERY LOW	CRITICAL
HbA1c % ≤6months (follow-up 6 months; Better indicated by lower values). [Ferguson 2001]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	33	33	-	MD 0.2 lower (0.64 lower to 0.24 higher)	VERY LOW	CRITICAL
Quality of Life ≤6months: DTSQ (follow-up 6 months) **MD and SD not given.** [Ferguson 2001]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	30	30	-	Unable to calculate MD[(d)(e)]	VERY LOW	CRITICAL
Quality of Life ≤6months: HFS (follow-up 6 months) **MD and SD not given.** [Ferguson 2001]												
1	Randomised trials	Very serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	30	30	-	Unable to calculate MD[(d)(e)]	VERY LOW	CRITICAL

(a) Information is from one study at very high risk of bias - unclear randomisation, unclear allocation concealment and no blinding. Crossover study with no washout period.
(b) 95% CI crosses both default MIDs (MIDs = 0.75 and 1.25)
(c) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -0.7 to -0.3; MID = ±0.5)
(d) Mean values and SD not given therefore unable to calculate MD and 95% CI
(e) Data given: No differences between Lispro and human insulin

Table 49: Clinical evidence profile: Education and relaxation of BG targets versus analogue insulin lispro/glargine

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Education	Analogue	Relative (95% CI)	Absolute	Quality	Importance
HbA1c % ≤6months (follow-up 24 weeks; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	7	7	-	MD 0.7 higher (0.2 lower to 1.6 higher)	LOW	CRITICAL
Altered hypoglycaemia awareness ≤6months (follow-up 24 weeks; assessed with: score ≥4 out of 7 on a validated questionnaire)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2/7 (28.6%)	4/7 57.1%	RR 0.5 (0.13 to 1.9)	285 fewer per 1000 (from 497 fewer to 514 more)	VERY LOW	CRITICAL
Quality of Life ≤6months: DQOL (follow-up 24 weeks; measured with: DQOL; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[e]	None	7	7	-	MD 12 lower (26.38 lower to 2.38 higher)	VERY LOW	CRITICAL
Quality of Life ≤6months: HFS (follow-up 24 weeks; measured with: Hypoglycaemia Fear Survey; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[f]	None	7	7	-	MD 2 lower (23.88 lower to 19.88 higher)	VERY LOW	CRITICAL

(a) Information is from one study at high risk of bias - unclear randomisation, unclear allocation concealment and blinding not mentioned (objective outcome)
(b) 95% CI crosses the upper default MID (95% CI for SMD used as only one study: -0.34 to 1.86; MID = ±0.5)
(c) Information is from one study at very high risk of bias - unclear randomisation, unclear allocation concealment and blinding not mentioned (subjective outcome)
(d) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)
(e) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.93 to 0.29; MID = ±0.5)
(f) 95% CI crosses both the default MIDs (95% CI for SMD used as only one study: -1.14 to 0.96; MID = ±0.5)

Table 50: Clinical evidence profile: Education and relaxation of BG targets versus CSII

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Education	CSII	Relative (95% CI)	Absolute		
HbA1c % ≤6months (follow-up 24 weeks; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	7	7	-	MD 0.9 higher (0.15 lower to 1.95 higher)	LOW	CRITICAL
Altered hypoglycaemia awareness ≤6months (follow-up 24 weeks; assessed with: score ≥4 out of 7 on a validated questionnaire)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Very serious[d]	None	2/7 (28.6%)	3/7 42.9%	RR 0.67 (0.16 to 2.84)	142 fewer per 1000 (from 360 fewer to 789 more)	VERY LOW	CRITICAL
Quality of Life ≤6months: DQOL (follow-up 24 weeks; measured with: DQOL; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[e]	None	7	7	-	MD 16 lower (34.97 lower to 2.97 higher)	VERY LOW	CRITICAL
Quality of Life ≤6months: HFS (follow-up 24 weeks; measured with: Hypoglycaemia Fear Survey; Better indicated by lower values)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[f]	None	7	7	-	MD 17 higher (1.25 to 32.75 higher)	VERY LOW	CRITICAL

(a) Information is from one study at high risk of bias - unclear randomisation, unclear allocation concealment and no blinding (objective outcome)
(b) 95% CI crosses the upper default MID (95% CI for SMD used as only one study: -0.27 to 1.95; MID = ±0.5)
(c) Information is from one study at very high risk of bias - unclear randomisation, unclear allocation concealment and no blinding (subjective outcome)
(d) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)
(e) 95% CI crosses the lower default MID (95% CI for SMD used as only one study: -1.94 to 0.28; MID = ±0.5)
(f) 95% CI crosses the upper default MID (95% CI for SMD used as only one study: -0.09 to 2.20; MID = ±0.5)

I.7 Ketone monitoring

I.7.1 Self-monitoring and in-hospital monitoring

Table 51: Clinical evidence profile: Blood β-HBA versus urine β-HBA ketone measurement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Blood β-HBA	Urine β-HBA (≤6 months)	Relative (95% CI)	Absolute		
HbA1c (follow-up 6 months; measured with: Laffel 2006; Better indicated by lower values)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious indirectness[b]	Serious[c]	None	62	61	-	MD 0.7 higher (0.12 to 1.08 higher)	VERY LOW	IMPORTANT
ER use (follow-up 6 months; assessed with: Laffel 2006)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious indirectness[b]	Serious[d]	None	8/62 (12.9%)	14/61 (23%)	RR 0.56 (0.25 to 1.24)	101 fewer per 1000 (from 172 fewer to 55 more)	VERY LOW	CRITICAL
Hospitalisation (follow-up 6 months; assessed with: Laffel 2006)												
1	Randomised trials	Very serious[a]	No serious inconsistency	Serious indirectness[b]	Very serious[e]	None	3/62 (4.8%)	8/61 (13.1%)	RR 0.37 (0.1 to 1.33)	83 fewer per 1000 (from 118 fewer to 43 more)	VERY LOW	CRITICAL

(a) Details not given for randomisation method, allocation concealment or blinding.
(b) Population is a mixture of children, adolescents and young adults (age ≤22 years)
(c) 95% CI crosses one of the MIDs (MID = ±0.7 ie. 0.5 x SD of 1.4)
(d) 95% CI crosses one of the MIDs (MID = 0.75 and 1.25)
(e) 95% CI crosses both of the MIDs (MID = 0.75 and 1.25)
(f) Arterial risk control

I.7.2 Aspirin

Table 52: Clinical evidence profile: Aspirin versus placebo (less than or equal to 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Placebo (≤6 months)	Relative (95% CI)	Absolute	Quality	Importance
HbA1c (follow-up 4 weeks; measured with: Hansen 2000; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	8	9	-	MD 0.1 lower (0.67 lower to 0.47 higher)	VERY LOW	IMPORTANT
Dyspepsia (follow-up 4 weeks; assessed with: Hansen 2000)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	3/8 (37.5%)	3/9 (33.3%)	RR 1.12 (0.31 to 4.07)	40 more per 1000 (from 230 fewer to 1000 more)	VERY LOW	IMPORTANT
Adverse events (follow-up 4 weeks; assessed with: Hansen 2000)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	-5	-5	-5	-5	VERY LOW	IMPORTANT

(a) Randomisation and allocation concealment details not given
(b) 95% CI crosses both MIDs (MID = ±0.3% that is, 0.5 x SD of 0.6%)
(c) 95% CI crosses both MIDs
(d) Number of events in each arm was not reported, therefore the RR and 95% CI were not estimable
(e) Study reported that there was NS difference between the groups

Table 53: Clinical evidence profile: Aspirin versus placebo (more than 6 months)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Aspirin	Placebo (>6 months, published and unpublished data)	Relative (95% CI)	Absolute	Quality	Importance
Mortality (all-cause) (follow-up mean 5 years; assessed with: ETDRS 1992)												
1	Randomised trials	No serious risk of bias1	No serious inconsistency	Serious[b]	Serious3	None	29/559 (5.2%)	39/571 (6.8%)	RR 0.76 (0.48 to 1.21)	16 fewer per 1000 (from 36 fewer to 14 more)	LOW	CRITICAL
Mortality (CV) (follow-up mean 5 years; assessed with: ETDRS unpublished type 1 diabetes, no previous CV events)												
1	Randomised trials	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	32/683 (4.7%)	40/710 (5.6%)	RR 0.83 (0.53 to 1.31)	10 fewer per 1000 (from 26 fewer to 17 more)	LOW	CRITICAL
CV events -all (follow-up mean 5 years; assessed with: ETDRS unpublished type 1 diabetes, no previous CV events)												
1	Randomised trials	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	55/683 (8.1%)	64/710 (9%)	RR 0.89 (0.63 to 1.26)	10 fewer per 1000 (from 33 fewer to 23 more)	LOW	CRITICAL
MI (fatal and non-fatal) (follow-up mean 5 years; assessed with: ETDRS unpublished type 1 diabetes, no previous CV events)												
1	Randomised trials	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	37/683 (5.4%)	48/710 (6.8%)	RR 0.80 (0.53 to 1.21)	14 fewer per 1000 (from 32 fewer to 14 more)	MODERATE	CRITICAL
Stroke (fatal and non-fatal) (follow-up mean 5 years; assessed with: ETDRS unpublished type 1 diabetes, no previous CV events)												
1	Randomised trials	No serious risk of	No serious inconsistency	No serious indirectness	Very serious[d]	None	17/683 (2.5%)	13/710 (1.8%)	RR 1.36 (0.67 to 2.78)	7 more per 1000 (from 6 fewer to	LOW	CRITICAL

		bias[a]								33 more)		

(a) Overall good: however, method of randomisation unclear
(b) 1 study (ETDRS) is mixed population of type 1 diabetes and type 2 diabetes as well as primary and secondary prevention
(c) 95% CI crosses one MID
(d) 95% CI crosses both MIDs

I.8 Inpatient management

I.8.1 IV insulin

Table 54: Clinical evidence profile: IV insulin versus SC insulin during surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV insulin	SC insulin (surgery)	Relative (95% CI)	Absolute		
Mild hypoglycaemia (follow-up 3 days; assessed with: ≥1 BG level <5 mmol/litre) [CHRISTIANSEN 1988]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	6/10 (60%)	40%	RR 1.5 (0.6 to 3.74)	200 more per 1000 (from 160 fewer to 1000 more)	VERY LOW	CRITICAL
Duration of inpatient stay (follow-up 3 days; Better indicated by lower values) [CHRISTIANSEN 1988]												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[c]	None	10	10	-	median 0 higher	VERY LOW	IMPORTANT
Achieving target BG levels (5-10 mmol/litre) during all 3 days (% of values within range)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	48%	26%	p<0.01[(d)]		VERY LOW	CRITICAL
Achieving target BG levels (5-10 mmol/litre) during the infusion period (% of values within range)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[d]	None	67%	28%	p<0.0001[(d)]		VERY LOW	CRITICAL

(a) Information is from one study at high risk of bias (allocation concealment unclear)
(b) 95% CI crosses both default MIDs (MID = 0.75 and 1.25)
(c) Data cannot be combined in a forest plot as reported as median and range
(d) Insufficient data provided to calculate mean difference and 95% CI for imprecision; only % and p-value given.

Table 55: Clinical evidence profile: IV insulin versus continuation of CSII (with supplemental SC or IV insulin if required) during surgery

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV insulin	SCII continuation	Relative (95% CI)	Absolute	Quality	Importance
Severe intra-op hypoglycaemia (assessed with: intra-op BG <40 mg/dl or loss of consciousness) [CORNEY 2012]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/20 (0%)	0%	-	-	LOW	CRITICAL

Table 56: Clinical evidence profile: IV insulin versus suspension of CSII (with or without IV or SC insulin bolus) during surgery

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IV insulin	Suspension of CSII	Relative (95% CI)	Absolute	Quality	Importance
Severe intra-op hypoglycaemia (assessed with: intra-op BG <40 mg/dl or loss of consciousness) [CORNEY 2012]												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/20 (0%)	0%	-	-	LOW	CRITICAL

I.8.1.1 Additional data

Corney et al., 2012[96,96] reported a SS difference between groups for:

- Percentage of patients achieving the intra-operative target BG
- Percentage of patients with intra-operative hypoglycaemia
- Percentage of patients with intra-operative hyperglycaemia

These outcomes were reported graphically and the comparison reported as P=0.034 but there was not enough data reported to combine in a meta-analysis.

I.9 Complications

I.9.1 Gastroparesis

Table 57: Clinical evidence profile: Metoclopramide versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Metoclopramide	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Symptom score (max 100 = worse) <6 months (measured with: RICCI 1985; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	13	13	-	MD 18.8 lower (46.18 lower to 8.58 higher)	LOW	IMPORTANT
Symptoms - felt better, no. of patients <6 months (assessed with: SNAPE)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	7/10 (70%)	0/10 (0%)	RR 15 (0.97 to 231.84)	-	VERY LOW	IMPORTANT
								0%		-		
No vomiting, no. of patients <6 months (assessed with: SNAPE)												
1	Randomised trials	Very serious[c]	No serious inconsistency	No serious indirectness	Serious[d]	None	6/10 (60%)	0/10 (0%)	RR 13 (0.83 to 203.83)	-	VERY LOW	CRITICAL
								0%		-		
Vomiting, no. of patients improving by score ≥2; <6 months (assessed with: MCCALLUM)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[e]	None	6/10 (60%)	4/8 (50%)	RR 1.2 (0.51 to 2.83)	100 more per 1000 (from 245 fewer to 915 more)	VERY LOW	CRITICAL
								50%		100 more per 1000 (from 245 fewer to 915 more)		
Weight loss, no. of patients <6 months (assessed with: SNAPE)												
1	Randomise	Very	No serious	No serious	Very	None	3/10	6/10	RR 0.5	300 fewer per	VERY	IMPORTANT

	d trials	serious[c]	inconsistency	indirectness	serious[e]		(30%)	(60%)	(0.17 to 1.46)	1000 (from 498 fewer to 276 more)	LOW	
								60%		300 fewer per 1000 (from 498 fewer to 276 more)		
Adverse events, no of patients <6 months (assessed with: SNAPE, MCCALLUM)												
2	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[f]	None	11/28 (39.3%)	23/32 (71.9%)	RR 0.59 (0.39 to 0.89)	295 fewer per 1000 (from 79 fewer to 438 fewer)	LOW	IMPORTANT
								60.5%		248 fewer per 1000 (from 67 fewer to 369 fewer)		

(a) Unclear details of randomisation and allocation concealment
(b) 95% CI crosses lower MID. MID = 17 (0.5 x SD 34)
(c) Unclear details of randomisation and allocation concealment; no wash-out period
(d) 95% CI crosses upper default MID (1.25)
(e) 95% CI crosses both default MIDs (0.75 and 1,25)
(f) No explanation was provided

Table 58: Clinical evidence profile: Domperidone versus placebo

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Domperidone**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
QoI (SF36) - Physical Component Scale (follow-up < 6 months; measured with: scale 0 - 100; Better indicated by higher values)												
1 Silvers 1998	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	104	99	-	MD 2.42 higher (2.21 to 2.63 higher)	MODERATE	IMPORTANT
QoI (SF36) - Mental Component Scale (follow-up < 6 months; measured with: Scale 0 - 100; Better indicated by higher values)												

1 Silvers 1998	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	104	99	-	MD 0.12 lower (0.4 lower to 0.16 higher)	MODERATE	IMPORTANT
Vomiting (follow-up < 6 months)												
1 Silvers 1998	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[b]	None	0/105 (0%)	5/103 (4.9%)	RR 0.09 (0 to 1.59)	44 fewer per 1000 (from 49 fewer to 29 more)	VERY LOW	CRITICAL
Vomiting (follow-up < 6 months)												
1 Braun 1989	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	13	13	There was NS difference between Domperidone and Placebo		LOW	CRITICAL
Adverse events (follow-up < 6 months)												
1 Silvers 1998	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	63/105 (60%)	65/103 (63.1%)	RR 0.09 (0 to 1.59)	574 fewer per 1000 (from 631 fewer to 372 more)	MODERATE	IMPORTANT
TSS frequency												
1 Braun 1989	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	13	13	Domperidone was SS better than placebo (p<0.05)		LOW	IMPORTANT
TSS intensity												
1 Braun 1989	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	13	13	Domperidone was SS better than placebo (p<0.05)		LOW	IMPORTANT

(a) Unclear randomisation (as details not given), allocation concealment not reported
(b) Confidence Interval crosses both ends of default MID (0.75, 1.25)
(c) Insufficient data reported; study only reports p-values.

Table 59: Clinical evidence profile: Domperidone versus metoclopramide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Domperidone	Metoclopramide	Relative (95% CI)	Absolute		
TSS - Symptom severity score (maximum 12) (follow-up 4 weeks; measured with: Patterson 1999; range of scores: 0-12; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	48	45	-	MD 0.38 lower (0.58 to 0.18 lower)	MODERATE	IMPORTANT
Vomiting - severity (maximum 3) (follow-up 4 weeks; measured with: Patterson 1999; range of scores: 0-3; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	48	45	NS difference between the treatment groups.		LOW	CRITICAL

(a) Unclear randomisation (as details not given), allocation concealment not reported
(b) Insufficient data reported - study only reports 'no significant difference' between groups

Table 60: Clinical evidence profile: Erythromycin versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Erythromycin	Control	Relative (95% CI)	Absolute		
Symptom severity score (maximum 3.0) (follow-up 2 weeks; measured with: SAMSOM 1997; range of scores: 0-3; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	12	12	-	MD 0.28 lower (0.9 lower to 0.34 higher)	LOW	IMPORTANT
Individual symptoms severity scores (maximum 3.0) (follow-up 2 weeks; measured with: SAMSOM 1997; range of scores: 0-3; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	Data not reported; just says NS improvement in any individual symptom score.				LOW	IMPORTANT

(a) Unclear allocation concealment
(b) 95% CI crosses one (lower) MID: MID = 0.5xSD of 0.86 (that is, 0.43)
(c) Details of the data were not reported in the study, thus unable to assess imprecision.

Table 61: Clinical evidence profile: BOTOX versus placebo

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	BoTOX	Control	Relative (95% CI)	Absolute	Quality	Importance
GCSI score reduction (maximum 45; lower better) (follow-up 1 months; measured with: FRIEDENBERG 2008; Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious indirectness[b]	Very serious[a]	None	16	16	-	MD 2.3 lower (11.62 lower to 7.02 higher)	VERY LOW	IMPORTANT

(a) 95% CI crosses both MIDs: MID = 0.5 x SD of 4.5 (that is, 2.3)
(b) Subgroup analysis of the diabetic patients from the randomised study

Table 62: Clinical evidence profile: Electrical stimulation (ON versus OFF)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Electrical stimulation	Control	Relative (95% CI)	Absolute	Quality	Importance
Total symptom severity score (TSS) - 6 symptoms (follow-up 1 months; measured with: ABELL 2003; range of scores: 0-24; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	17	17	-	MD 1.9 lower (2.98 to 0.82 lower)	LOW	IMPORTANT
Total symptom severity score (TSS) - 7 symptoms (follow-up 3 months; measured with: MCCALLUM 2010B; range of scores: 0-28; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	45	45	-	MD 1.08 higher (1.65 lower to 3.81 higher)	LOW	IMPORTANT
Total symptom frequency score (TSS) - 7 symptoms (follow-up 3 months; measured with: MCCALLUM 2010B; range of scores: 0-28; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	45	45	-	MD 0.61 higher (2.4 lower to 3.62 higher)	MODERATE	IMPORTANT
Vomiting severity score (follow-up 3 months; measured with: MCCALLUM 2010B; range of scores: 0-4; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[d]	None	45	45	-	MD 0.42 higher (0.1 lower to 0.94 higher)	LOW	CRITICAL

Vomiting frequency (episodes/day) (follow-up 1 months; measured with: FROKJAER 2008; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Very serious[e]	None	7	7	-	MD 0.8 higher (0.21 lower to 1.81 higher)	VERY LOW	CRITICAL
Vomiting frequency score (follow-up 3 months; measured with: MCCALLUM 2010B; range of scores: 0-4; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	45	45	-	MD 0.28 higher (0.32 lower to 0.88 higher)	MODERATE	CRITICAL
Weekly vomiting frequency; episodes/week (follow-up 1 month; measured with: ABELL 2003 Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	Serious imprecision[f]	None	Median 6.0 (IQR 3.0-14.8)	Median 12.8 (5.5-24.2)	-	-	VERY LOW	CRITICAL
Weekly vomiting frequency; episodes/week (follow-up 3 months; measured with: MCCALLUM 2010B; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious imprecision[f]	None	Median 3.8 (IQR 0.75-14.0)	Median 4.3 (0.4-15.1)	-	-	LOW	CRITICAL
Vomiting score (follow-up 3 days; measured with: ABELL 2011 range of scores: 1-5; Better indicated by lower values)												
1	Randomised trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	-0.31 units/day (-0.64, 0.02) with stimulation (p=0.069)				LOW	CRITICAL

(a) Unclear allocation concealment
(b) Subgroup analysis of the diabetic patients from the randomised study
(c) 95% CI crosses one MID (upper); MID = 0.5xSD of 6.47 (that is, 3.23)
(d) 95% CI crosses one MID (upper): MID = 0.5 x SD of 1.27 (that is, 0.64)
(e) 95% CI crosses both MIDs: MID = 0.5 x SD of 0.34 (that is, 0.17)
(f) Only median and IQR values were reported in the study, thus unable to assess imprecision.

I.9.2 Acute painful neuropathy

None

Appendix J: Forest plots

J.1 Diagnosis

J.1.1 Distinguishing between different types of diabetes

None

J.2 Education programmes and self-care

J.2.1 Structured education programmes

J.2.1.1 Structured education programme versus control - usual care or other type of education (less than or equal to 6 months)

Figure 1: HbA1c % – all studies pooled

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BGATIII -Schachinger 2005	6.93	1.02	56	6.95	0.98	55	16.3%	-0.02 [-0.39, 0.35]
DAFNE (Amiel 2002)	8.4	1.2	67	9.4	1.3	72	13.0%	-1.00 [-1.42, -0.58]
DEWEERT 1991	-0.25	2.8	355	-0.1	1.4	203	18.5%	-0.15 [-0.50, 0.20]
HYPOS -Hermans 2007	7.2	0.8	80	7.1	0.9	72	30.5%	0.10 [-0.17, 0.37]
ROSSI 2010	-0.4	0.9	67	-0.5	1	63	21.0%	0.10 [-0.23, 0.43]
TERENT 1985	10.1	1.7	9	10	2	10	0.8%	0.10 [-1.56, 1.76]
Total (95% CI)			**634**			**475**	**100.0%**	**-0.11 [-0.26, 0.04]**

Heterogeneity: Chi² = 21.82, df = 5 (P = 0.0006); I² = 77%
Test for overall effect: Z = 1.42 (P = 0.15)

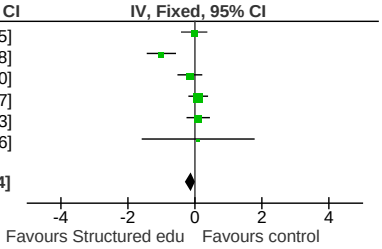


Figure 2: HbA1c % – subgroup analysis (by type of comparison)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Structured education vs. usual care								
DAFNE (Amiel 2002)	8.4	1.2	67	9.4	1.3	72	8.0%	-1.00 [-1.42, -0.58]
DEWEERT 1991	-0.25	2.8	355	-0.1	1.4	203	11.3%	-0.15 [-0.50, 0.20]
TERENT 1985	10.1	1.7	9	10	2	10	0.5%	0.10 [-1.56, 1.76]
Subtotal (95% CI)			**431**			**285**	**19.7%**	**-0.49 [-0.75, -0.22]**
Heterogeneity: Chi² = 9.91, df = 2 (P = 0.007); I² = 80%								
Test for overall effect: Z = 3.61 (P = 0.0003)								
1.2.2 Structured education vs. other education / support								
BGATIII -Schachinger 2005	6.93	1.02	56	6.95	0.98	55	9.9%	-0.02 [-0.39, 0.35]
HYPOS -Hermans 2007	7.2	0.8	80	7.1	0.9	72	18.6%	0.10 [-0.17, 0.37]
PRIMAS 2013	-0.4	1	81	0	0.6	79	21.2%	-0.40 [-0.65, -0.15]
ROSSI 2010	-0.4	0.9	67	-0.5	1	63	12.8%	0.10 [-0.23, 0.43]
ROSSI 2013	-0.48	0.8	64	-0.49	0.8	63	17.8%	0.01 [-0.27, 0.29]
Subtotal (95% CI)			**348**			**332**	**80.3%**	**-0.07 [-0.20, 0.06]**
Heterogeneity: Chi² = 9.36, df = 4 (P = 0.05); I² = 57%								
Test for overall effect: Z = 1.00 (P = 0.32)								
Total (95% CI)			**779**			**617**	**100.0%**	**-0.15 [-0.27, -0.03]**
Heterogeneity: Chi² = 27.07, df = 7 (P = 0.0003); I² = 74%								
Test for overall effect: Z = 2.50 (P = 0.01)								
Test for subgroup differences: Chi² = 7.80, df = 1 (P = 0.005), I² = 87.2%								

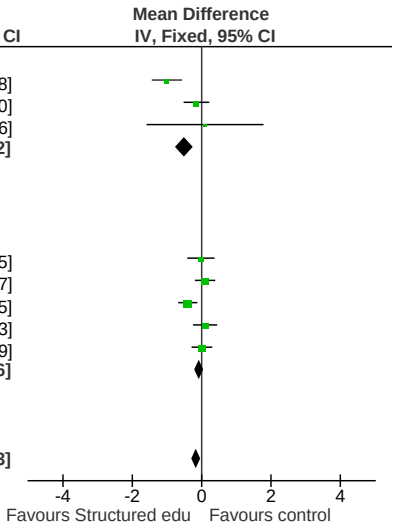


Figure 3: HbA1c % – subgroup analysis (carbohydrate counting included in the education)

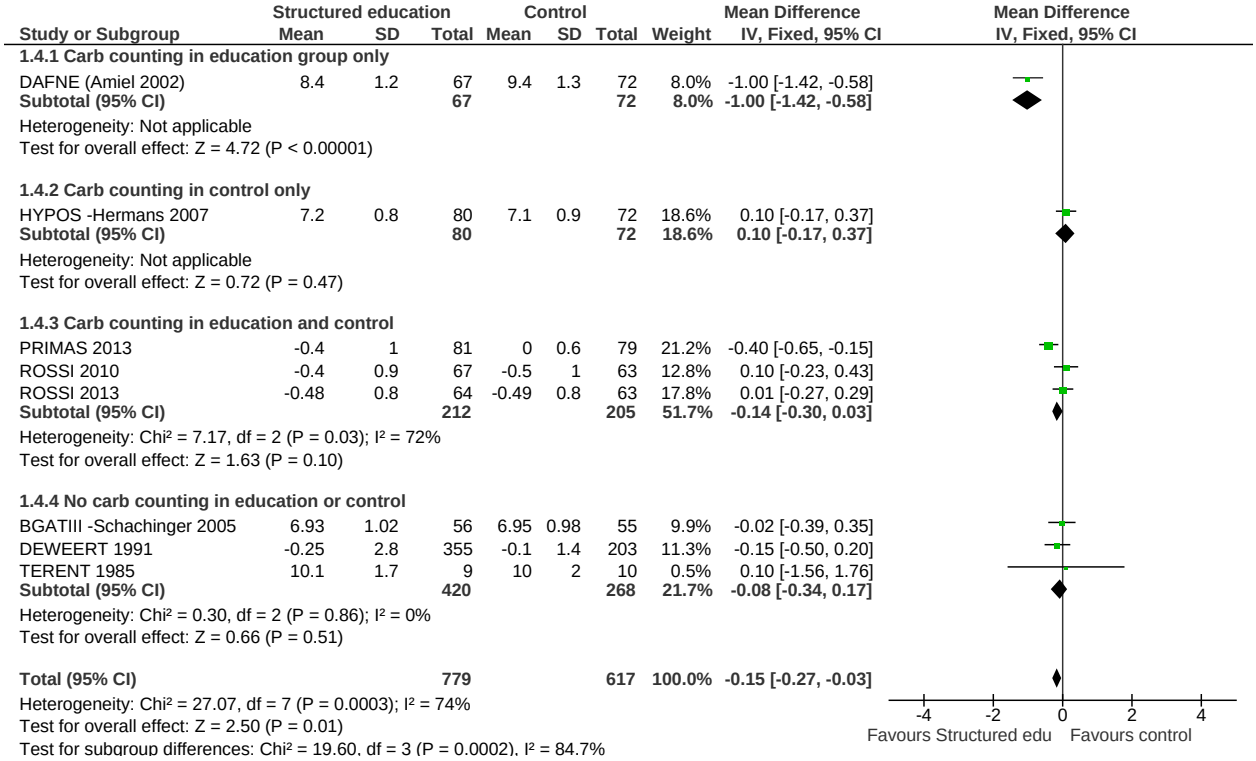
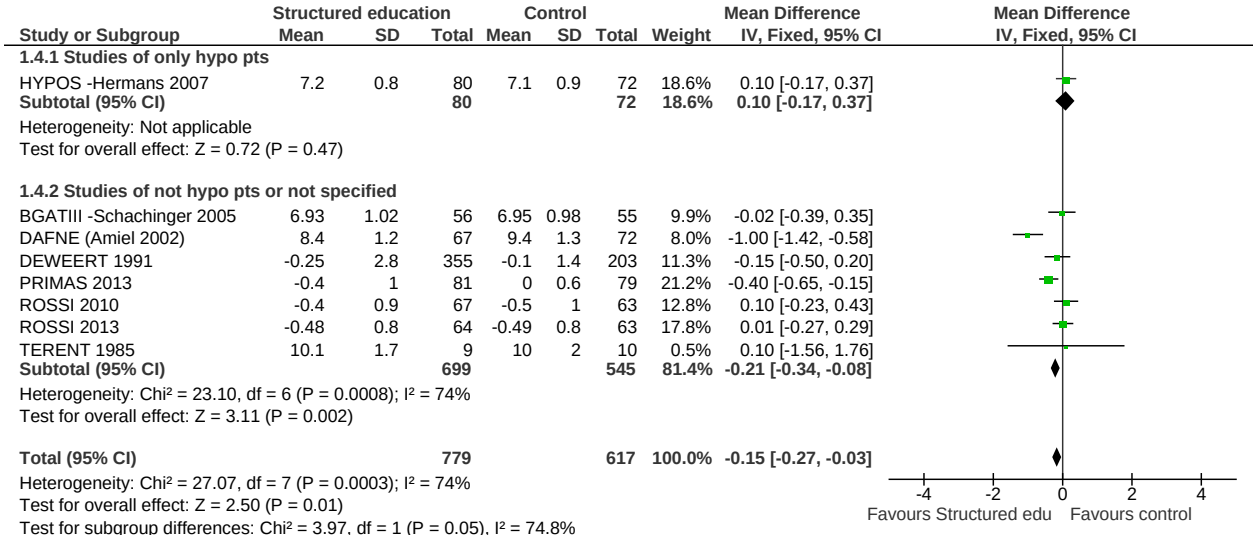


Figure 4: HbA1c % – subgroup analysis (studies with hypoglycaemic patients)



HbA1c, % - MD only given

No forest plot – data unsuitable

HbA1c, % - SD not given

No forest plot – data unsuitable

Figure 5: Severe hypoglycaemia (episodes / study)

Study or Subgroup	Favours Structured edu Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
DAFNE (Amiel 2002)	12	67	11	72	100.0%	1.21 [0.49, 2.96]
ROSSI 2010	0	67	0	63		Not estimable
Total (95% CI)		**134**		**135**	**100.0%**	**1.21 [0.49, 2.96]**
Total events	12		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)

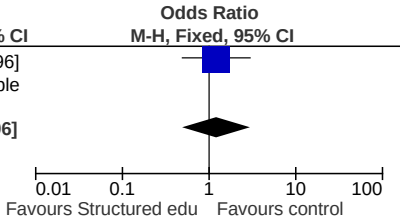


Figure 6: Severe hypoglycaemia (episodes/6 months)

Study or Subgroup	Structured edu Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BGATIII -Schachinger 2005	0.13	0.33	56	1.07	2.85	55	100.0%	-0.94 [-1.70, -0.18]
Total (95% CI)			**56**			**55**	**100.0%**	**-0.94 [-1.70, -0.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.02)

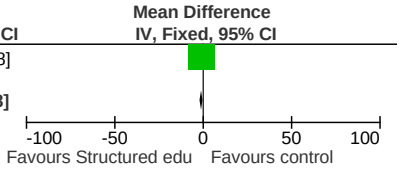


Figure 7: Severe hypoglycaemia (episodes/month)

Study or Subgroup	Structured edu Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
DEWEERT 1991	-0.05	0.9	355	-0.1	0.00001	203	100.0%	0.05 [-0.04, 0.14]
Total (95% CI)			**355**			**203**	**100.0%**	**0.05 [-0.04, 0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.30)

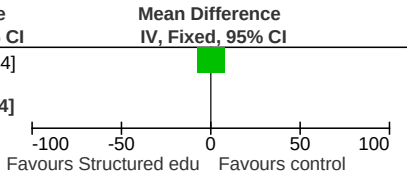
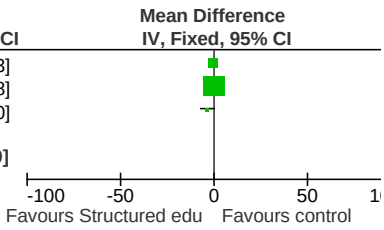


Figure 8: Severe hypoglycaemia (episodes/patient-year)

Study or Subgroup	Structured edu Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYPOS -Hermans 2007	0.9	1.9	74	1.2	2	72	26.7%	-0.30 [-0.93, 0.33]
PRIMAS 2013	-0.2	0.9	81	-0.3	1.5	79	72.4%	0.10 [-0.28, 0.48]
ROSSI 2013	45.6	9.8	64	49.2	10.3	63	0.9%	-3.60 [-7.10, -0.10]
Total (95% CI)			**219**			**214**	**100.0%**	**-0.04 [-0.37, 0.29]**

Heterogeneity: Chi² = 5.14, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 0.23 (P = 0.81)



Severe hypoglycaemia (episodes / person) - SD not given

No forest plot – data unsuitable

Figure 9: ADDQoL - impact

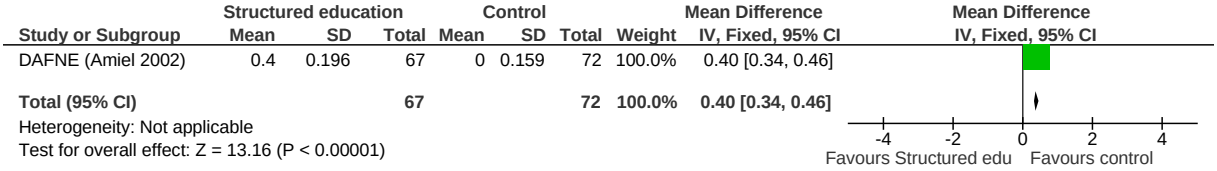


Figure 10: ADDQoL - impact and importance

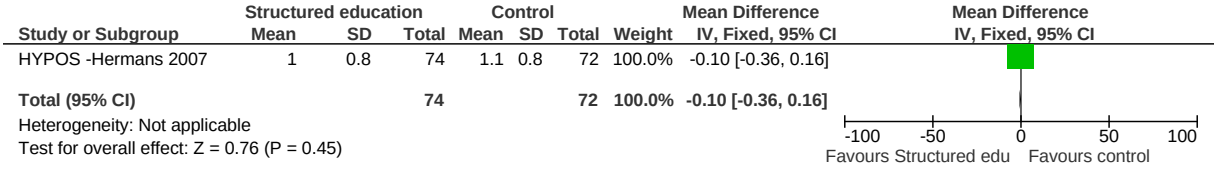


Figure 11: DTSQ - total satisfaction

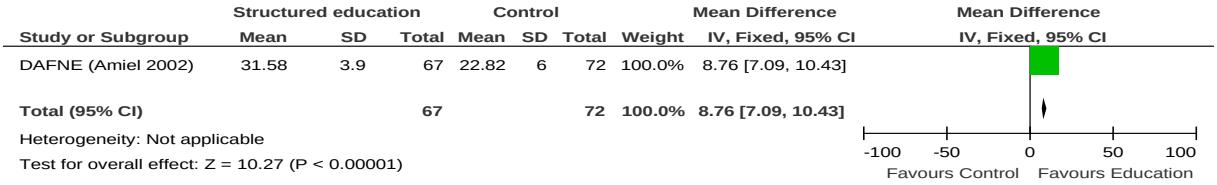
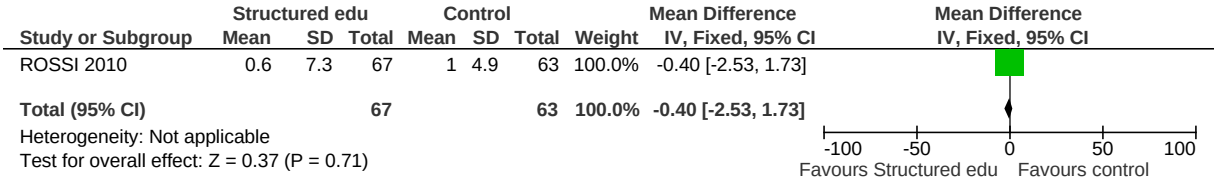


Figure 12: SF-36 physical



SF-36 physical health - MD only given

No forest plot – data unsuitable

Figure 13: SF-36 mental

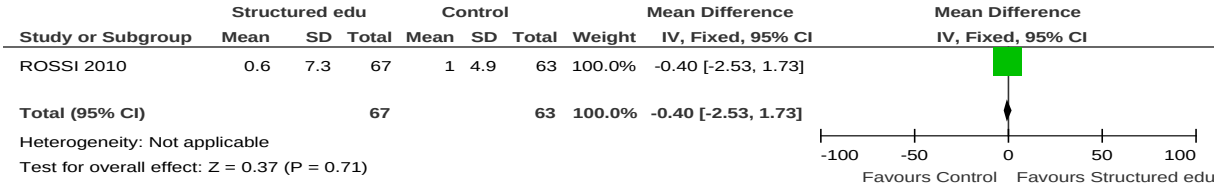


Figure 14: Hospital admissions

Study or Subgroup	Structured education Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ROSSI 2010	0	67	0	63		Not estimable
Total (95% CI)		**67**		**63**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

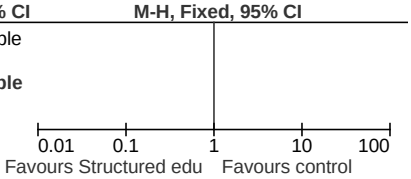


Figure 15: Symptomatic hypoglycaemia (perceived frequency, scale 0-6)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
DAFNE (Amiel 2002)	2.16	1.3	67	2.4	1.3	72	100.0%	-0.24 [-0.67, 0.19]
Total (95% CI)			**67**			**72**	**100.0%**	**-0.24 [-0.67, 0.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

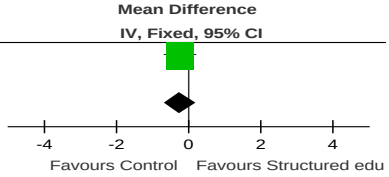


Figure 16: Hypoglycaemia unawareness (> recognition of low blood glucose, % patients)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BGATIII -Schachinger 2005	58.2	24.8	56	45.8	28.7	55	100.0%	12.40 [2.41, 22.39]
Total (95% CI)			**56**			**55**	**100.0%**	**12.40 [2.41, 22.39]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.01)

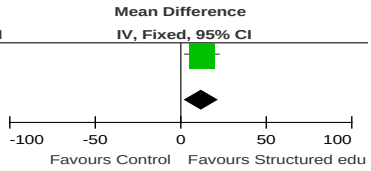


Figure 17: Hypoglycaemia awareness (HAQ)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYPOS -Hermans 2007	0.3	1.1	74	0.6	1.2	72	100.0%	-0.30 [-0.67, 0.07]
Total (95% CI)			**74**			**72**	**100.0%**	**-0.30 [-0.67, 0.07]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

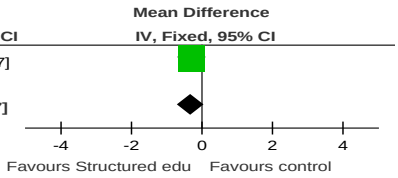
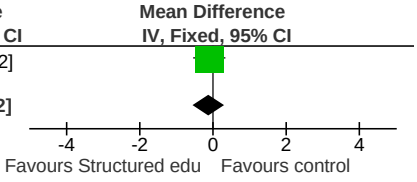


Figure 18: Hypoglycaemia unawareness (change in Clarke score, max 7)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
PRIMAS 2013	-0.5	1.4	81	-0.4	1.3	79	100.0%	-0.10 [-0.52, 0.32]
Total (95% CI)			**81**			**79**	**100.0%**	**-0.10 [-0.52, 0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)



Hypoglycaemia unawareness (VAS)

No forest plot – data unsuitable

Hypoglycaemia unawareness (% detection of low blood glucose)

No forest plot – data unsuitable

Figure 19: Fear of hypo (Hypo fear survey) - Worry

	Structured education			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
BGATIII -Schachinger 2005	15.2	12.1	56	14.6	12.2	55	100.0%	0.60 [-3.92, 5.12]
Total (95% CI)			**56**			**55**	**100.0%**	**0.60 [-3.92, 5.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.79)

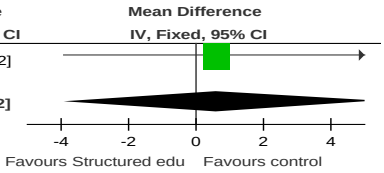


Figure 20: Fear of hypo (Hypo fear survey) – Behaviour

	Structured education			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
BGATIII -Schachinger 2005	13.7	8.2	56	11.6	6.4	55	100.0%	2.10 [-0.63, 4.83]
Total (95% CI)			**56**			**55**	**100.0%**	**2.10 [-0.63, 4.83]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)

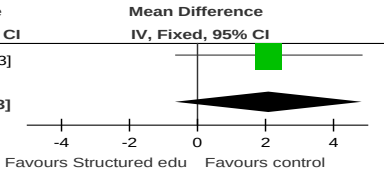
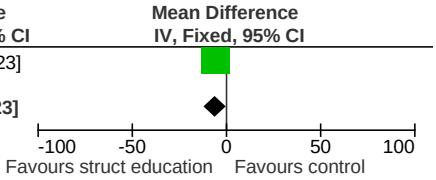


Figure 21: Fear of hypo (change in DSQoL)

	Struct Education			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
ROSSI 2013	-3.91	17.8	64	2.03	17.7	63	100.0%	-5.94 [-12.11, 0.23]
Total (95% CI)			**64**			**63**	**100.0%**	**-5.94 [-12.11, 0.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.89 (P = 0.06)



Fear of hypoglycaemia (hypoglycaemia fear survey) – Worry – MD only given

No forest plot – data unsuitable

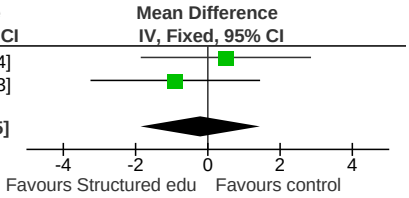
Fear of hypoglycaemia (hypoglycaemia fear survey) – Behaviour – MD only given

No forest plot – data unsuitable

Figure 22: Depression (CES-D)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYPOS -Hermans 2007	12.6	7.4	74	12.1	7	72	49.8%	0.50 [-1.84, 2.84]
PRIMAS 2013	-1.2	7.9	81	-0.3	7.1	79	50.2%	-0.90 [-3.23, 1.43]
Total (95% CI)			**155**			**151**	**100.0%**	**-0.20 [-1.85, 1.45]**

Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)



Depression (CES-D) - no SD given

No forest plot – data unsuitable

Figure 23: Anxiety (STAI)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYPOS -Hermans 2007	37.6	6.5	74	37.1	6.1	72	100.0%	0.50 [-1.54, 2.54]
Total (95% CI)			**74**			**72**	**100.0%**	**0.50 [-1.54, 2.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

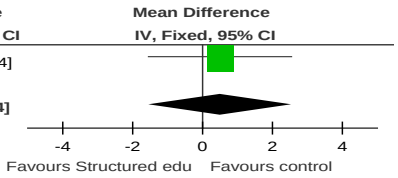
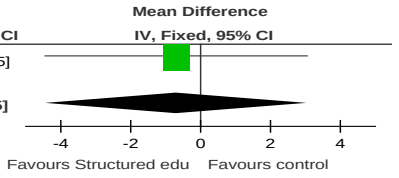


Figure 24: PAID

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HYPOS -Hermans 2007	23.3	11.7	74	24	11.4	72	100.0%	-0.70 [-4.45, 3.05]
Total (95% CI)			**74**			**72**	**100.0%**	**-0.70 [-4.45, 3.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)



PAID - no SD given

No forest plot – data unsuitable

Figure 25: Knowledge (% correct answers)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
KORHONEN 1983	79.5	1.9	39	72	2	38	100.0%	7.50 [6.63, 8.37]
Total (95% CI)			**39**			**38**	**100.0%**	**7.50 [6.63, 8.37]**

Heterogeneity: Not applicable
Test for overall effect: Z = 16.86 (P < 0.00001)

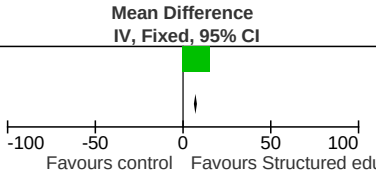


Figure 26: Knowledge (change score out of 11)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
PRIMAS 2013	0.7	1.6	81	0.6	1.6	79	100.0%	0.10 [-0.40, 0.60]
Total (95% CI)			**81**			**79**	**100.0%**	**0.10 [-0.40, 0.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)

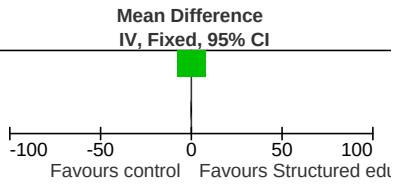
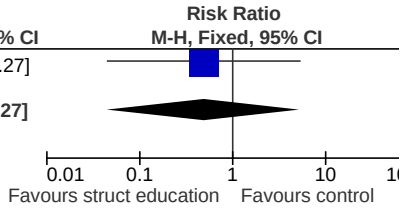


Figure 27: Adherence

Study or Subgroup	Structured education Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PRIMAS 2013	1	81	2	79	100.0%	0.49 [0.05, 5.27]
Total (95% CI)		**81**		**79**	**100.0%**	**0.49 [0.05, 5.27]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)



J.2.1.2 Structured education programme vs. control - usual care or other type of education (more than or equal to 12 months)

Figure 28: HbA1c %

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
BGATIII -Schachinger 2005	6.93	0.96	56	6.94	0.94	55	6.3%	-0.01 [-0.36, 0.34]
LENNON 1990	10.5	0.3	31	11.6	0.4	25	22.0%	-1.10 [-1.29, -0.91]
TERENT 1985	10.2	2.1	9	10.4	2.1	10	0.2%	-0.20 [-2.09, 1.69]
TRENTO 2005	-0.38	9.87	30	-0.4	1.15	28	0.1%	0.02 [-3.54, 3.58]
TRENTO 2011	0.21	0.18	27	-0.24	0.22	29	71.4%	0.45 [0.35, 0.55]
Total (95% CI)			**153**			**147**	**100.0%**	**0.08 [-0.01, 0.17]**

Heterogeneity: Chi² = 197.72, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.72 (P = 0.08)

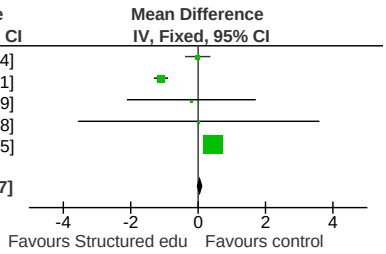


Figure 29: HbA1c % – subgroup analysis (by type of comparison)

Study or Subgroup	Structured education Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.2.1 Structured education vs. usual care								
LENNON 1990	10.5	0.3	31	11.6	0.4	25	22.0%	-1.10 [-1.29, -0.91]
TERENT 1985	10.2	2.1	9	10.4	2.1	10	0.2%	-0.20 [-2.09, 1.69]
Subtotal (95% CI)			**40**			**35**	**22.2%**	**-1.09 [-1.28, -0.90]**
Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 11.37 (P < 0.00001)								
2.2.2 Structured education vs. other education / support								
BGATIII -Schachinger 2005	6.93	0.96	56	6.94	0.94	55	6.3%	-0.01 [-0.36, 0.34]
TRENTO 2005	-0.38	9.87	30	-0.4	1.15	28	0.1%	0.02 [-3.54, 3.58]
TRENTO 2011	0.21	0.18	27	-0.24	0.22	29	71.4%	0.45 [0.35, 0.55]
Subtotal (95% CI)			**113**			**112**	**77.8%**	**0.41 [0.31, 0.51]**
Heterogeneity: Chi² = 6.03, df = 2 (P = 0.05); I² = 67%								
Test for overall effect: Z = 8.03 (P < 0.00001)								
Total (95% CI)			**153**			**147**	**100.0%**	**0.08 [-0.01, 0.17]**
Heterogeneity: Chi² = 197.72, df = 4 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 1.72 (P = 0.08)								
Test for subgroup differences: Chi² = 190.83, df = 1 (P < 0.00001), I² = 99.5%								

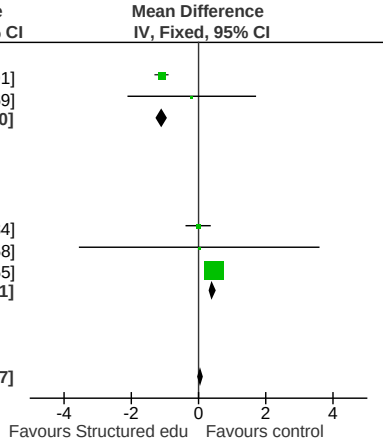


Figure 30: HbA1c % – subgroup analysis (carbohydrate counting included in the education)

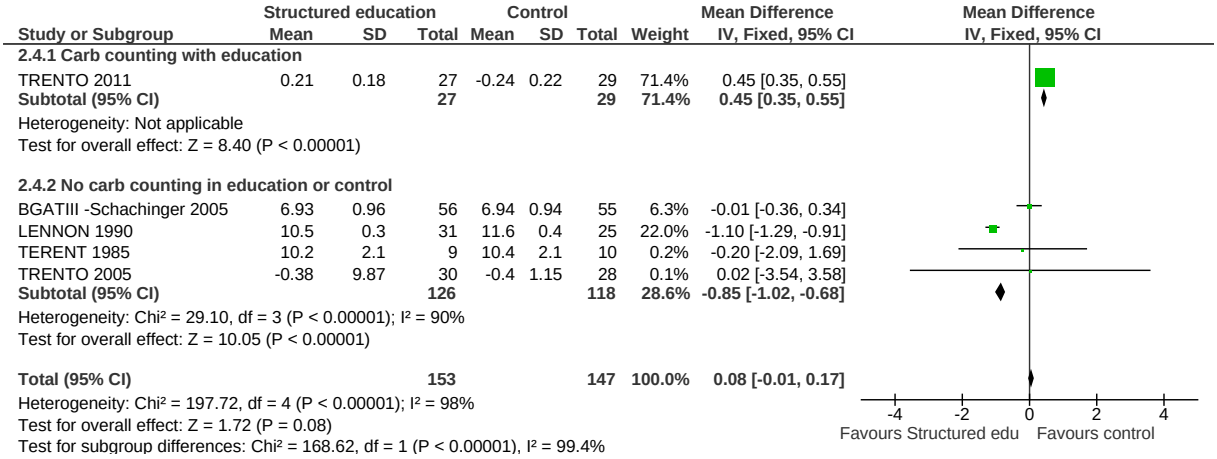
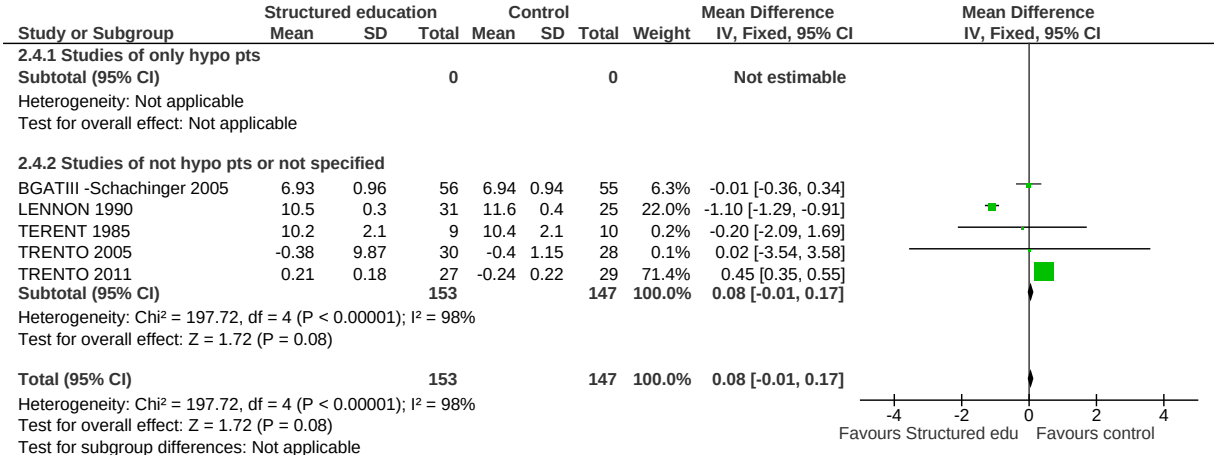


Figure 31: HbA1c % – subgroup analysis (studies with hypoglycaemic patients)



HbA1c % (between 6 and 12 months)

No forest plot – data unsuitable

HbA1c, % - MD only given

No forest plot – data unsuitable

Figure 32: Severe hypoglycaemia (episodes/study)

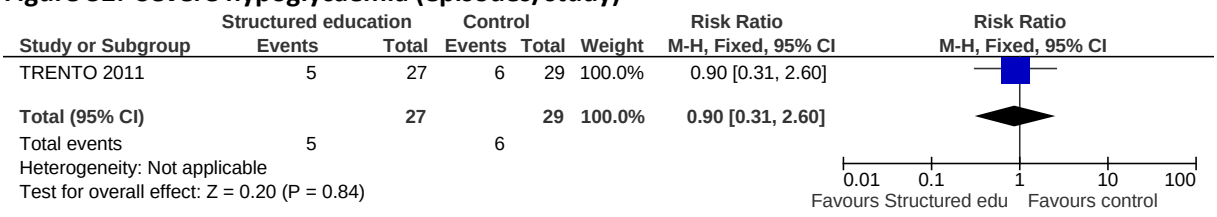
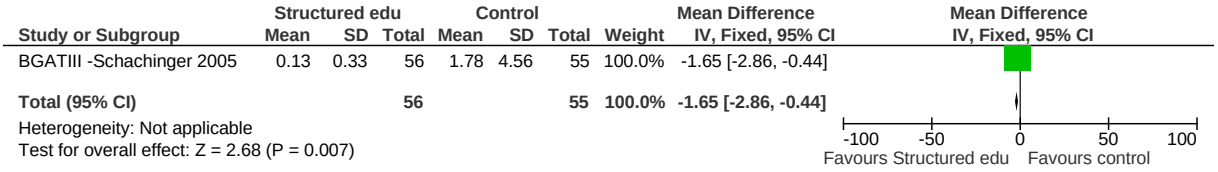


Figure 33: Severe hypoglycaemia (episodes/6 months)



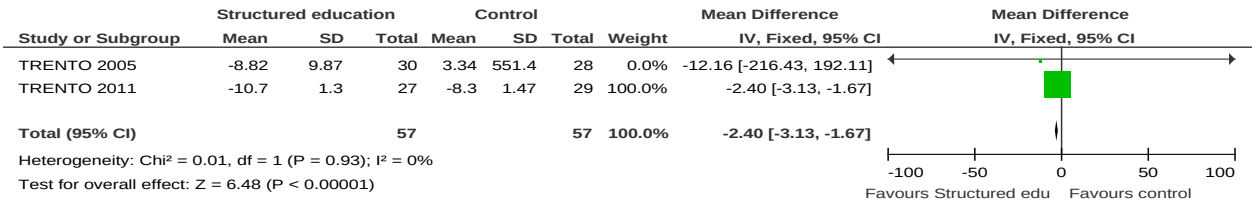
Severe hypoglycaemia (episodes/12 months) – SD not given

No forest plot – data unsuitable

Severe hypoglycaemia (episodes / person) - SD not given

No forest plot – data unsuitable

Figure 34: DQoL



SF-36 physical health - MD only given

No forest plot – data unsuitable

Figure 35: Hypoglycaemia unawareness (increased recognition of low blood glucose, % patients)

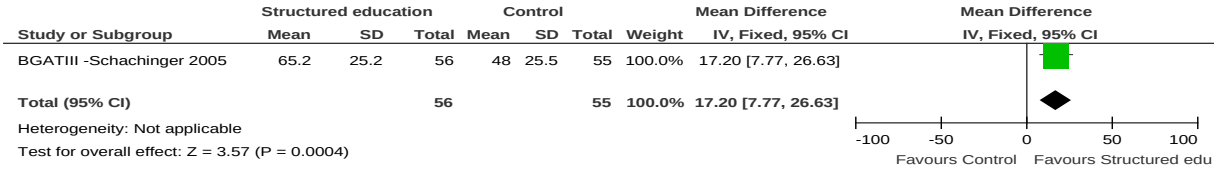


Figure 36: Fear of hypoglycaemia (hypoglycaemia fear survey) - Worry

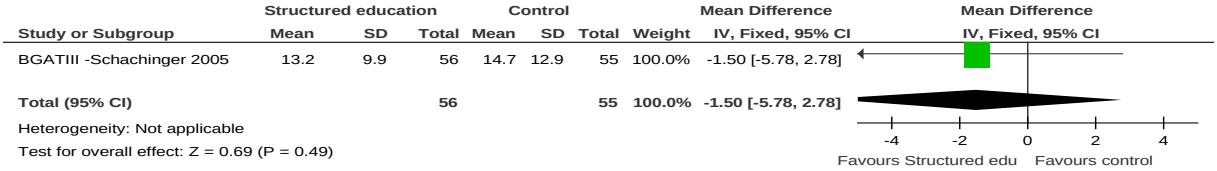
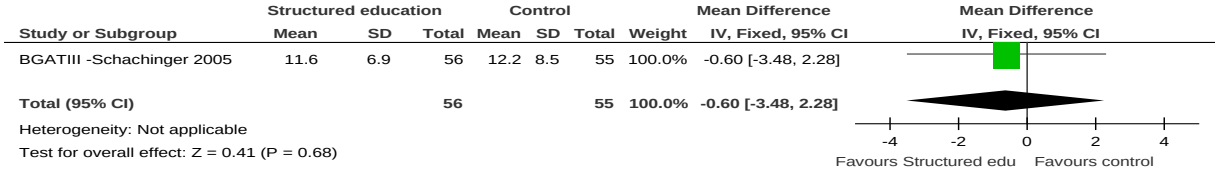


Figure 37: Fear of hypoglycaemia (hypoglycaemia fear survey) - Behaviour



Fear of hypoglycaemia (hypoglycaemia fear survey) – Worry – MD only given

No forest plot – data unsuitable

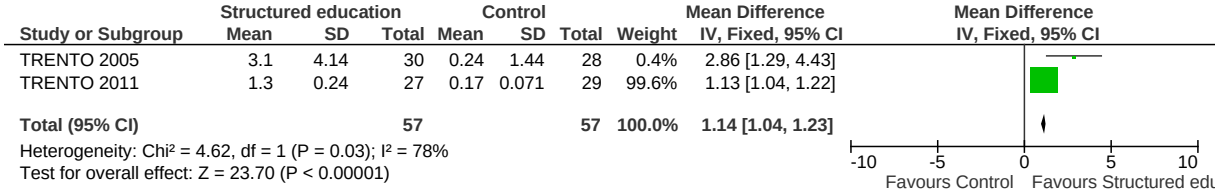
Fear of hypoglycaemia (hypoglycaemia fear survey) – Behaviour – MD only given

No forest plot – data unsuitable

Depression (CES-D) - no SD given

No forest plot – data unsuitable

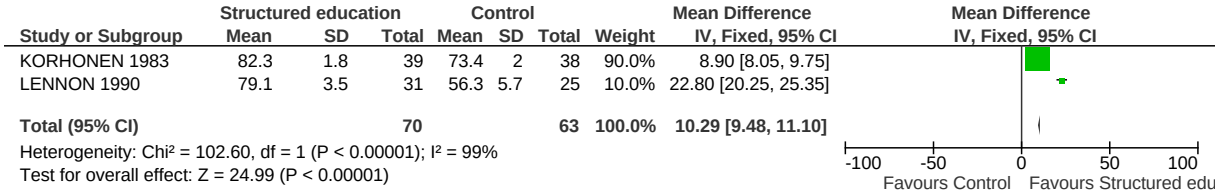
Figure 38: Knowledge of diabetes (GISED)



PAID - no SD given

No forest plot – data unsuitable

Figure 39: Knowledge (% correct answers)



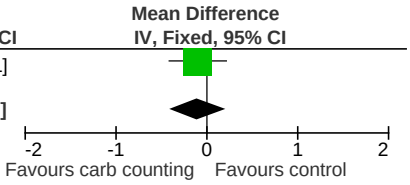
J.2.2 Carb counting

J.2.2.1 Carbohydrate counting versus no carbohydrate counting

Figure 40: HbA1c more than 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Scavone 2010	7.4	0.9	73	7.5	1.5	156	100.0%	-0.10 [-0.41, 0.21]
Total (95% CI)			**73**			**156**	**100.0%**	**-0.10 [-0.41, 0.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

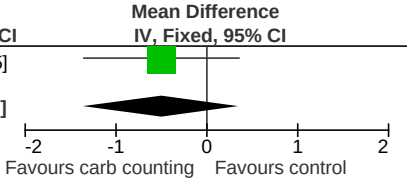


Note: Reported as SS difference (P<0.01) between groups for change score (not enough data provided to report change score and CI in meta-analysis and GRADE)

Figure 41: HbA1c less than or equal to 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schmidt 2012	8.4	0.9	21	8.9	1.1	8	100.0%	-0.50 [-1.35, 0.35]
Total (95% CI)			**21**			**8**	**100.0%**	**-0.50 [-1.35, 0.35]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)



Note: HbA1c change scores reported as NS different between groups for Laurenzi 2011 but not enough data reported from Laurenzi 2011 to include data in meta-analysis

Figure 42: Mild hypoglycaemia > 6 months

Study or Subgroup	Carb counting Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Scavone 2010	3	73	11	156	100.0%	0.58 [0.17, 2.03]
Total (95% CI)		**73**		**156**	**100.0%**	**0.58 [0.17, 2.03]**
Total events	3		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.40)

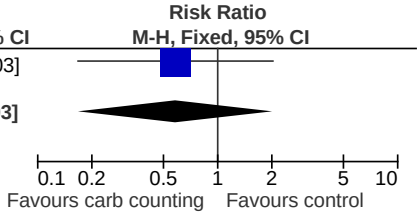


Figure 43: Severe hypoglycaemia less than or equal to 6 months

Study or Subgroup	Favours carb counting Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Laurenzi 2011	0	30	0	31		Not estimable
Schmidt 2012	2	21	1	8	100.0%	0.76 [0.08, 7.29]
Total (95% CI)		**51**		**39**	**100.0%**	**0.76 [0.08, 7.29]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

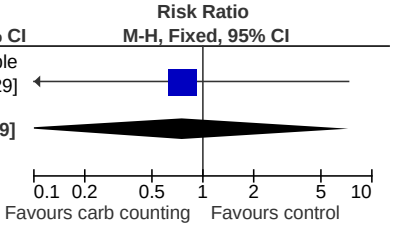


Figure 44: Hypoglycaemia fear survey less than or equal to 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schmidt 2012	22.8	13.8	21	24.5	18.2	8	100.0%	-1.70 [-15.62, 12.22]
Total (95% CI)			**21**			**8**	**100.0%**	**-1.70 [-15.62, 12.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)

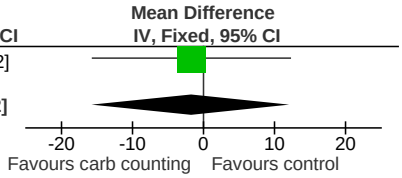


Figure 45: Problem areas in diabetes questionnaire less than or equal to 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schmidt 2012	28	19.2	21	27.2	18.8	8	100.0%	0.80 [-14.60, 16.20]
Total (95% CI)			**21**			**8**	**100.0%**	**0.80 [-14.60, 16.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)

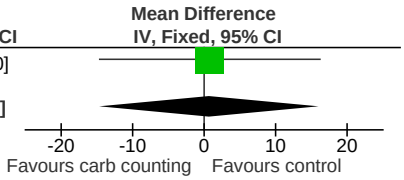


Figure 46: Audit of Diabetes Dependent QOL questionnaire less than or equal to 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schmidt 2012	-1.8	1.6	21	-1.4	0.9	8	100.0%	-0.40 [-1.33, 0.53]
Total (95% CI)			**21**			**8**	**100.0%**	**-0.40 [-1.33, 0.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.40)

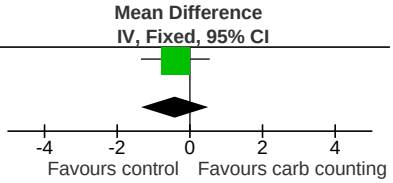
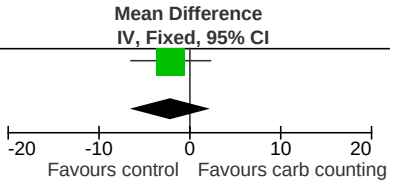


Figure 47: Diabetes Treatment Satisfaction Questionnaire less than or equal to 6 months

Study or Subgroup	carb counting Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Schmidt 2012	26.4	6	21	28.5	5.1	8	100.0%	-2.10 [-6.47, 2.27]
Total (95% CI)			**21**			**8**	**100.0%**	**-2.10 [-6.47, 2.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)



J.2.2.2 Bolus calculator versus manual carbohydrate counting

Figure 48: HbA1c less than or equal to 6 months

Study or Subgroup	Bolus calculator Mean	SD	Total	Manual carb counting Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Maurizi 2011	7.05	1.06	20	7.73	1.06	20	6.3%	-0.68 [-1.34, -0.02]
Schmidt 2012	8.1	0.4	22	8.4	0.9	21	15.4%	-0.30 [-0.72, 0.12]
Ziegler 2013	-0.7	0.7	105	-0.5	0.7	113	78.3%	-0.20 [-0.39, -0.01]
Total (95% CI)			**147**			**154**	**100.0%**	**-0.25 [-0.41, -0.08]**

Heterogeneity: Chi² = 1.97, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)

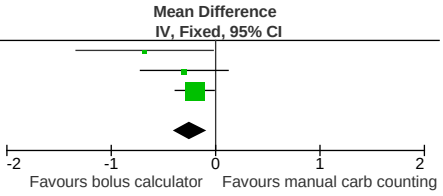


Figure 49: Mild hypoglycaemia less than or equal to 6 months

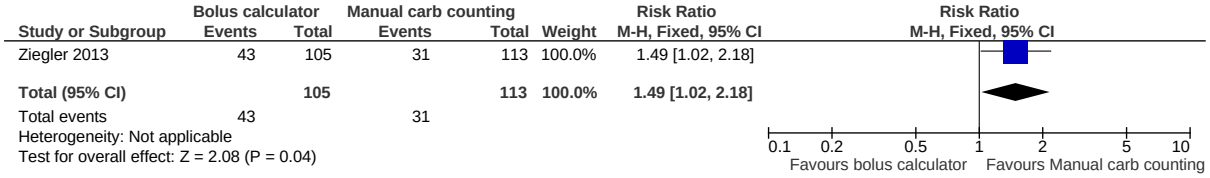


Figure 50: Severe hypoglycaemia less than or equal to 6 months

Figure 51: Hypoglycaemia fear survey less than or equal to 6 months

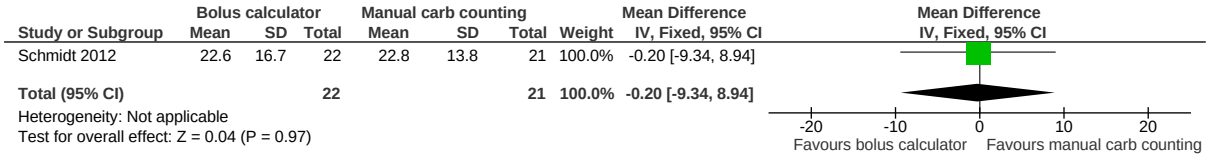


Figure 52: Problem areas in diabetes questionnaire less than or equal to 6 months

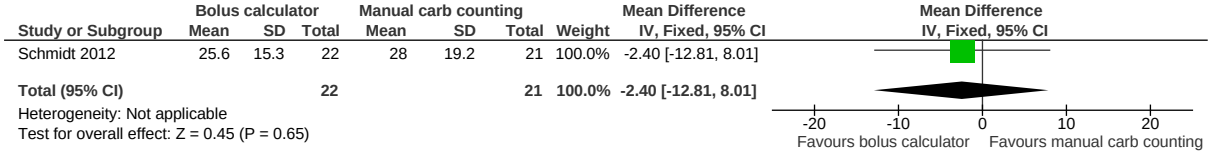


Figure 53: Audit of Diabetes Dependent QOL questionnaire less than or equal to 6 months

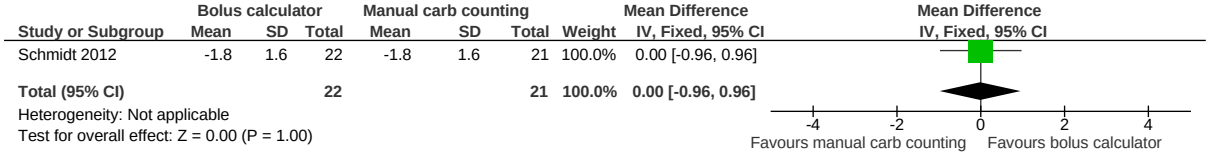
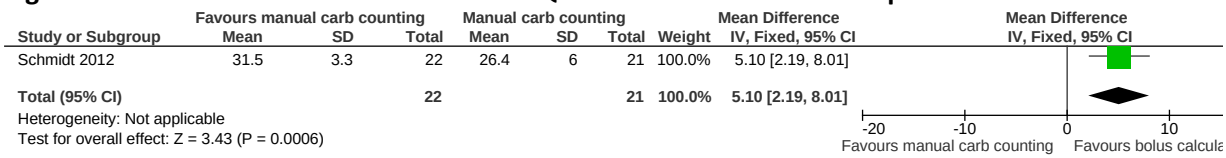


Figure 54: Diabetes Treatment Satisfaction Questionnaire less than or equal to 6 months



J.3 Blood glucose monitoring

J.3.1 HbA1c

None

J.3.2 SMBG targets, timing and frequency

None

J.3.3 SMBG technologies

J.3.3.1 Bolus calculator versus standard bolus for SMBG (less than 6 months follow-up)

Figure 55: HbA1c (%)

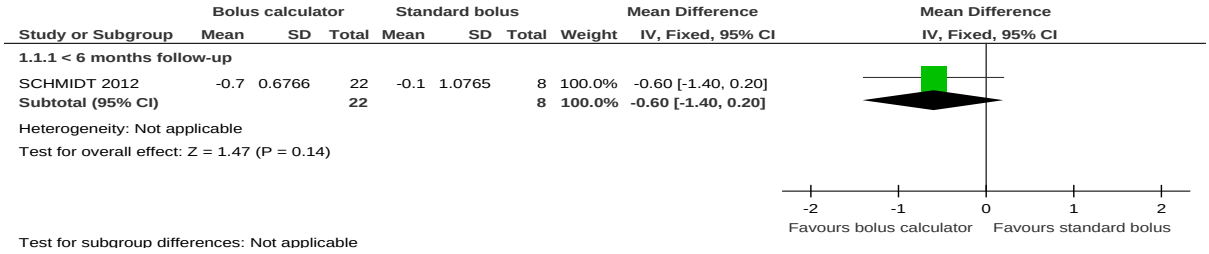
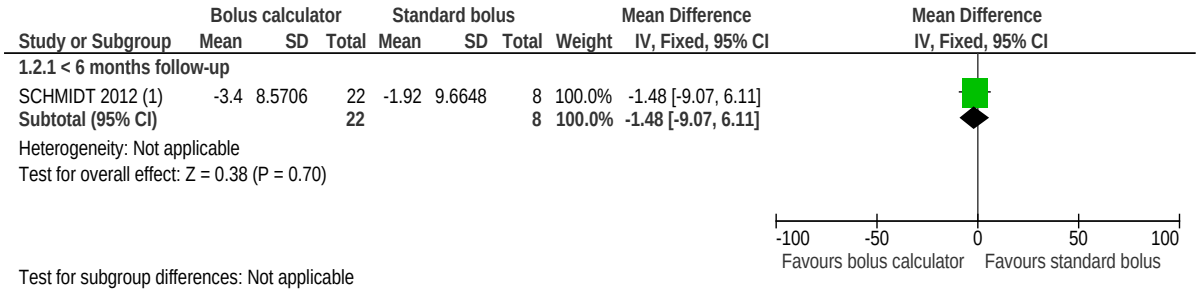
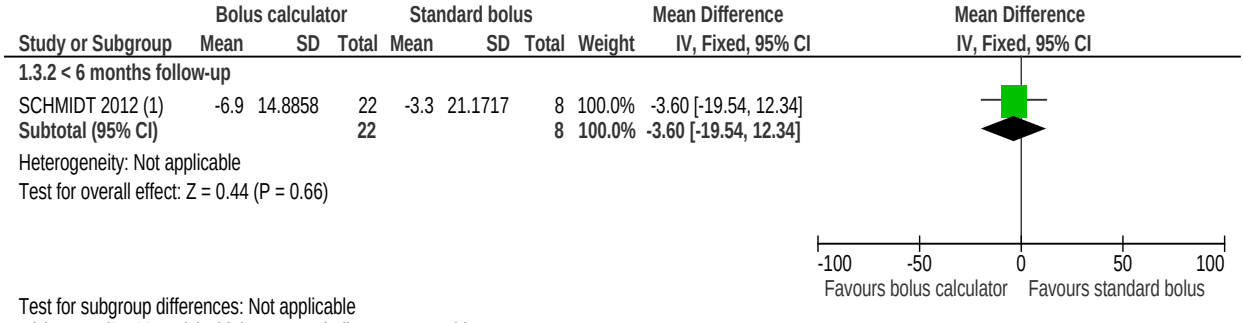


Figure 56: Hypoglycaemia Fear Survey (HFS)



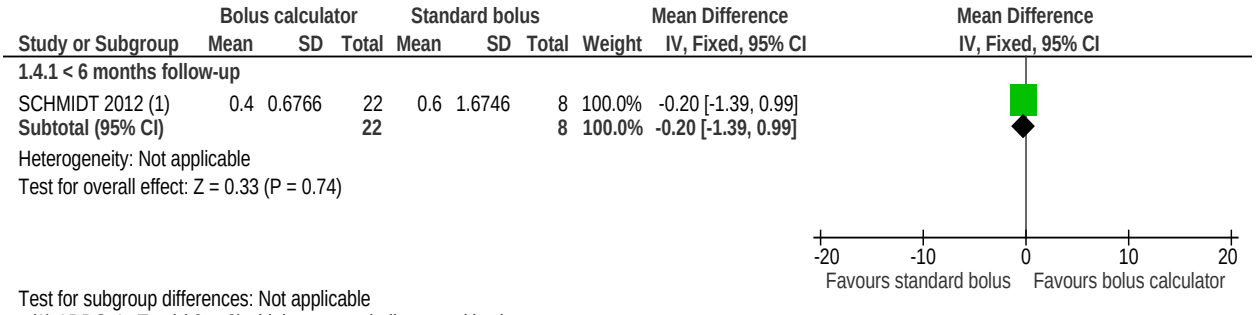
(1) HFS: Scores transformed to 0-100 scale. Higher scores indicate more fear.

Figure 57: Problem Areas in Diabetes (PAID)



(1) PAID: (0-100 scale) - higher scores indicate more problems.

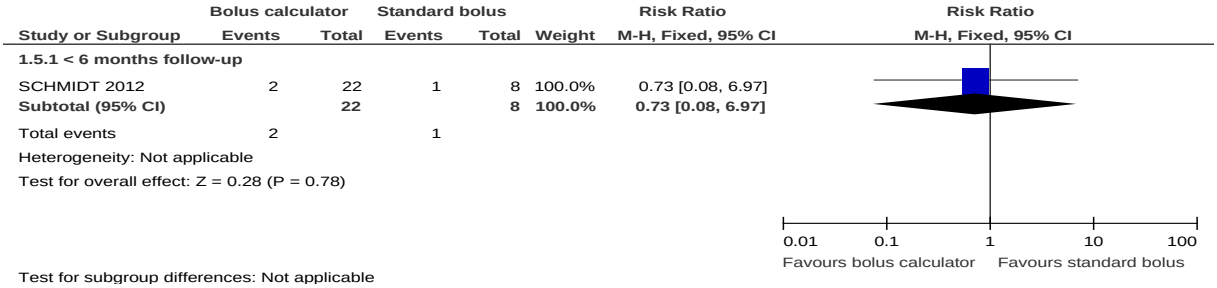
Figure 58: Audit of Diabetes-Dependent QoL (ADDQoL)



Test for subgroup differences: Not applicable

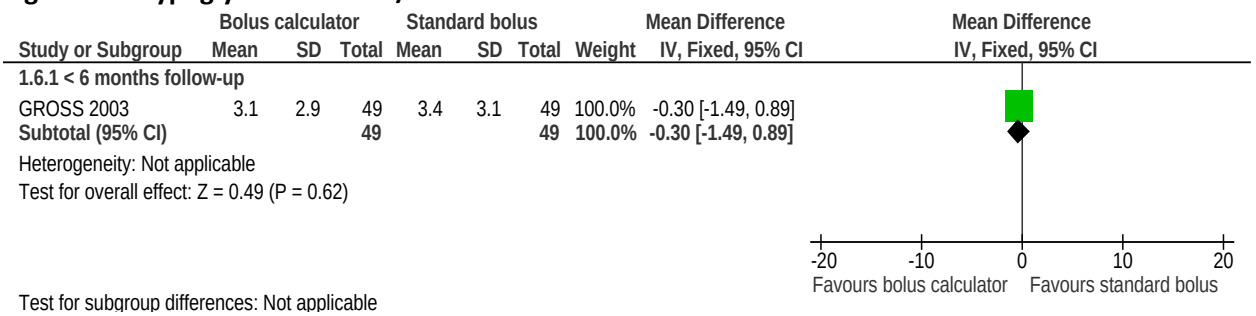
(1) ADDQoL: Total (-9 to 9) - higher scores indicate positive impact.

Figure 59: Severe hypoglycaemia



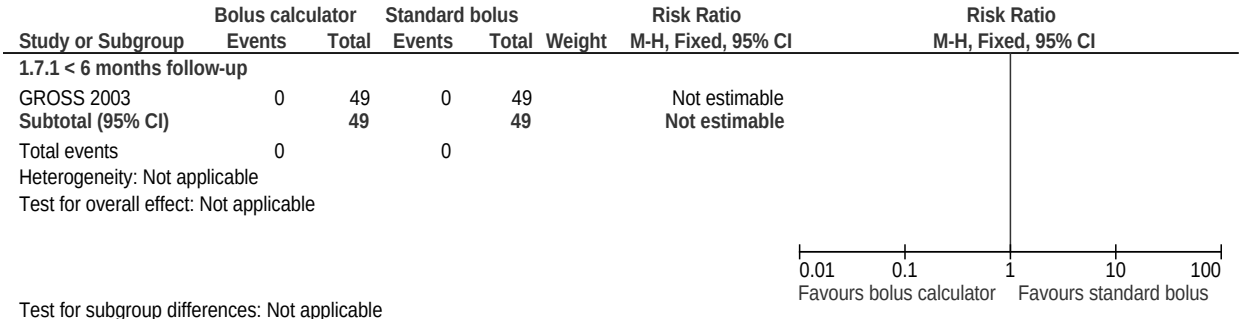
Test for subgroup differences: Not applicable

Figure 60: Hypoglycaemic event/week



Test for subgroup differences: Not applicable

Figure 61: Adverse events



J.3.1 SMBG versus CGM

J.3.1.1 Retrospective CGM versus care without CGM (with SMBG).

Figure 62: HbA1c (%) – Follow up less than or equal to 6 months

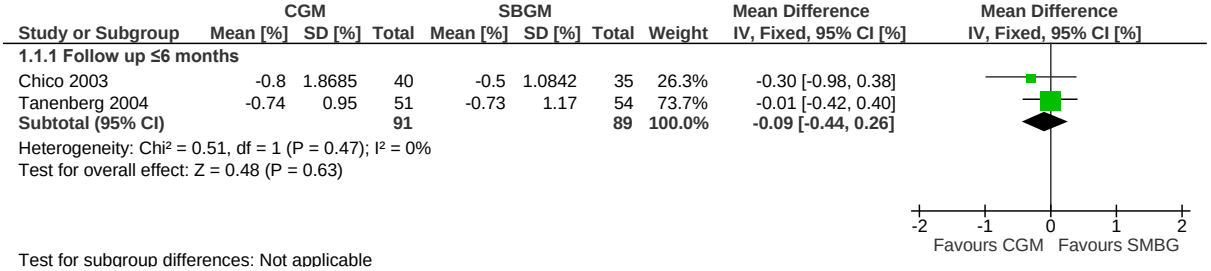


Figure 63: Percentage change in HbA1c (%) – follow-up more than 6 months

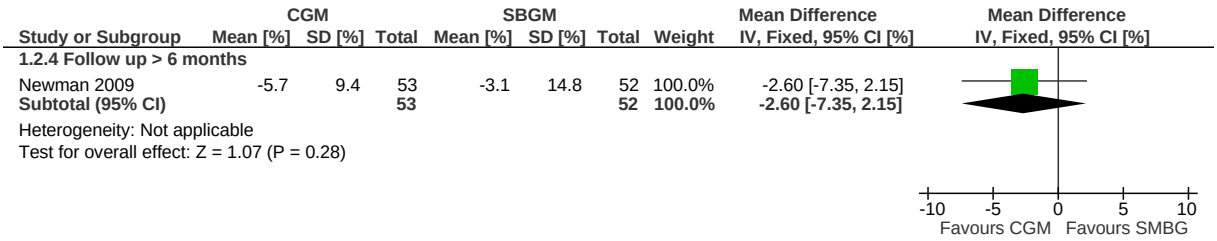
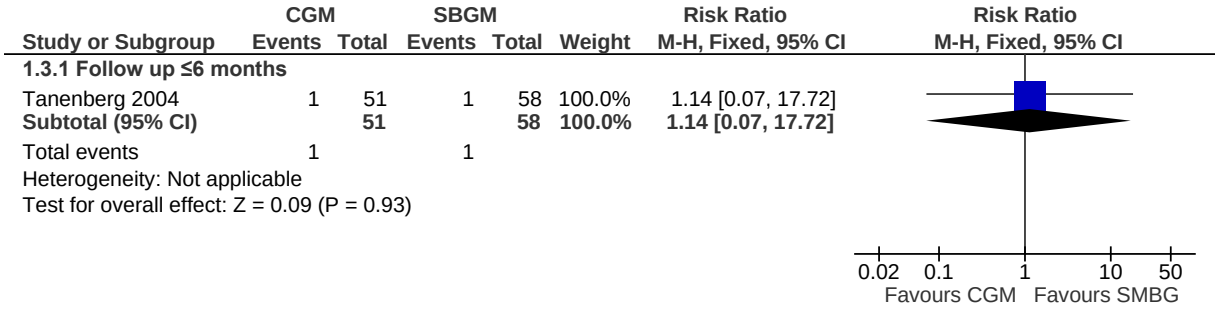
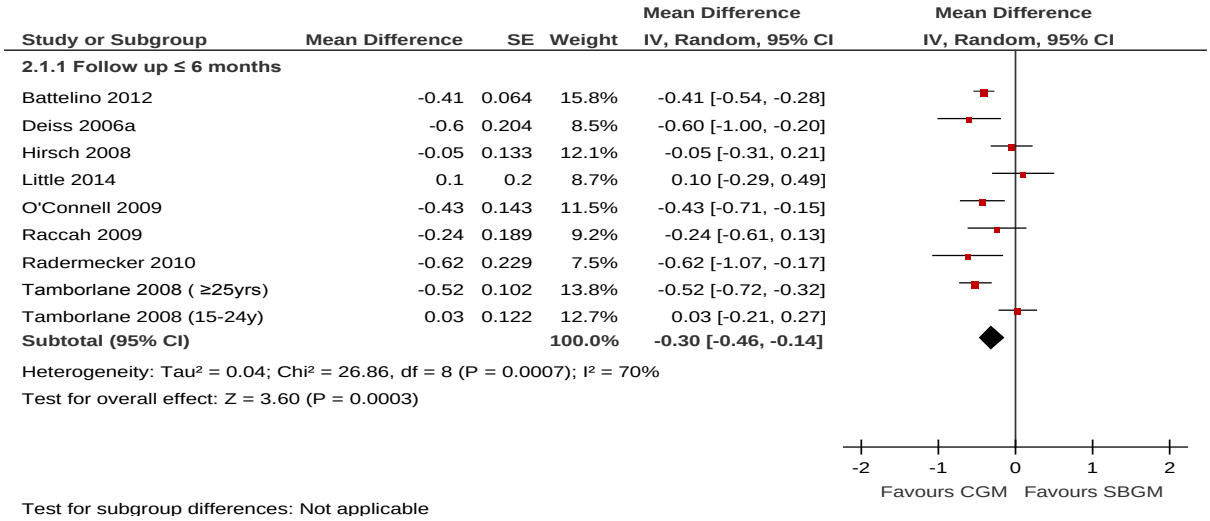


Figure 64: Severe hypoglycaemia – follow-up less than or equal to 6 months



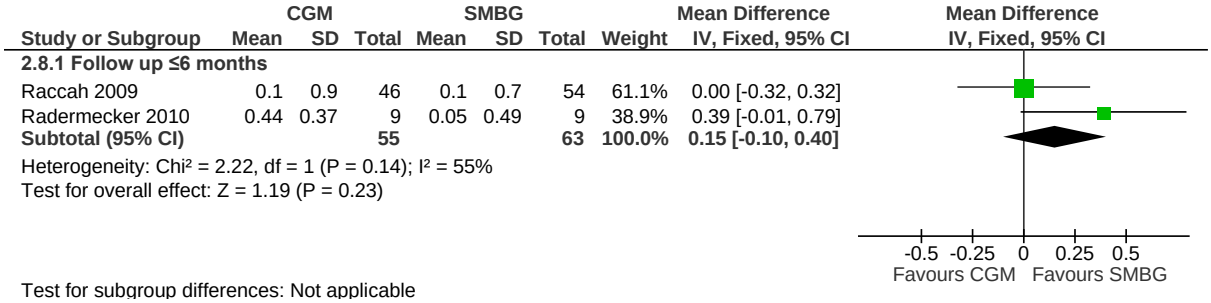
J.3.1.2 Real time CGM versus care without CGM (with SMBG)

Figure 65: HbA1c (%) – follow up less than or equal to 6 months



Test for subgroup differences: Not applicable

Figure 66: Hypoglycaemia (episodes/day) – follow up less than or equal to 6 months



Test for subgroup differences: Not applicable

Figure 67: Severe hypoglycaemia (episode/100 patient-years)– follow-up less than or equal to 6 months

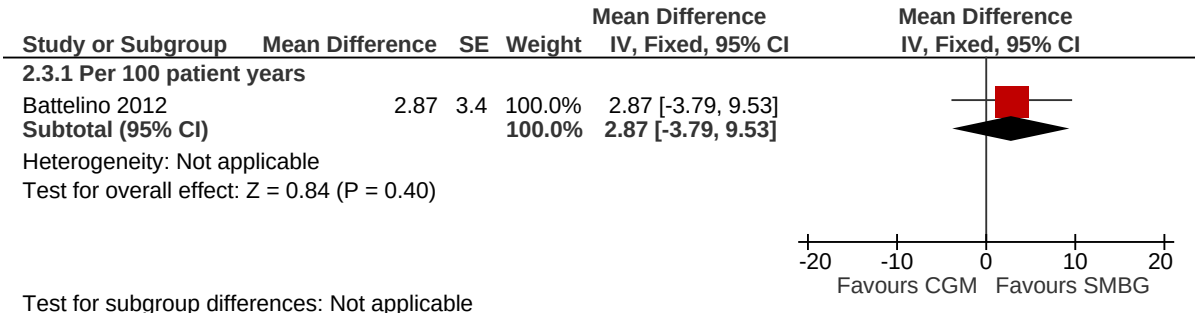


Figure 68: Severe hypoglycaemia (number of patients) – follow-up less than or equal to 6 months

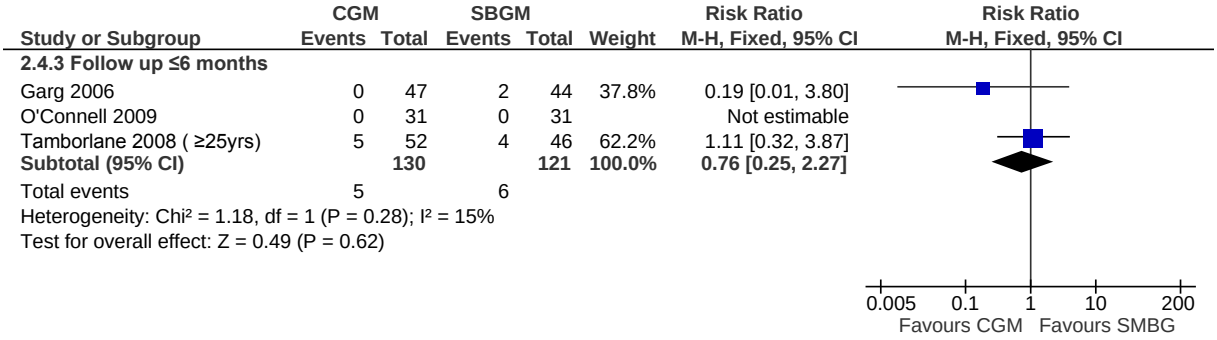


Figure 69: Severe hypoglycaemia (annualised rate: patient-year) – follow-up less than or equal to 6 months

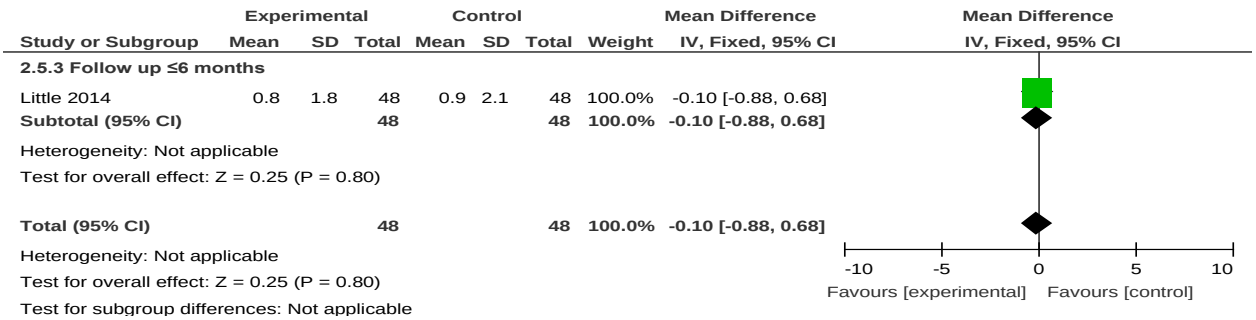


Figure 70: Quality of life: SF12 (Scale 0-100) – follow-up less than or equal to 6 months

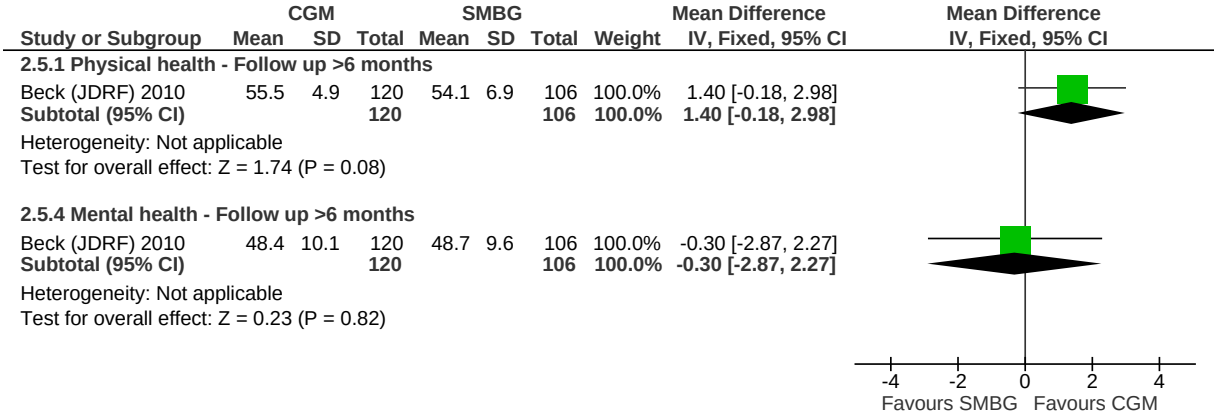


Figure 71: Quality of life: SF12 (Scale 0-100) – follow-up less than or equal to 6 months

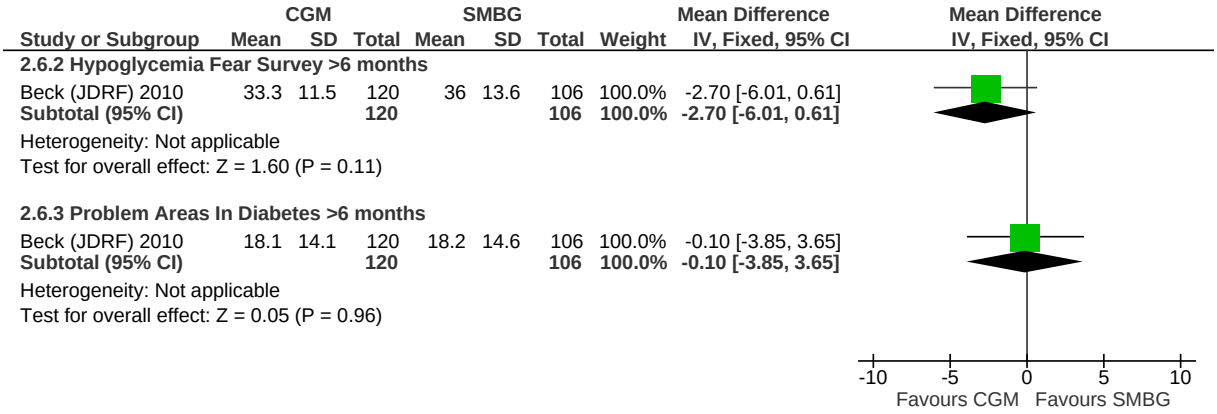


Figure 72: Quality of life total score (scale 0 – 100) – follow up less than or equal to 6 months

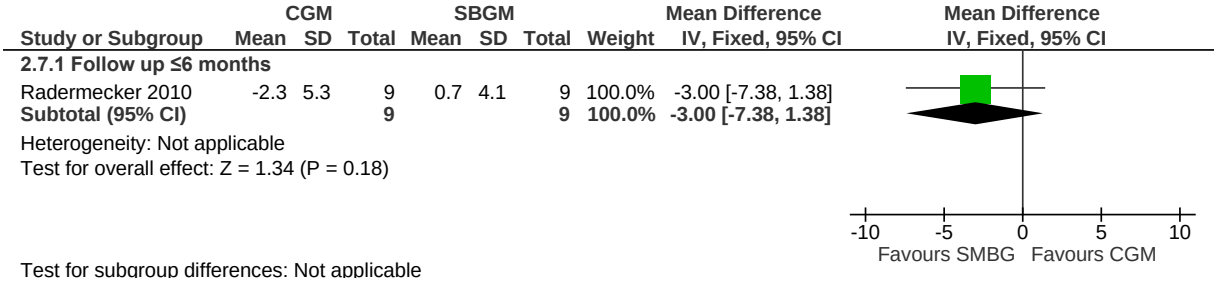
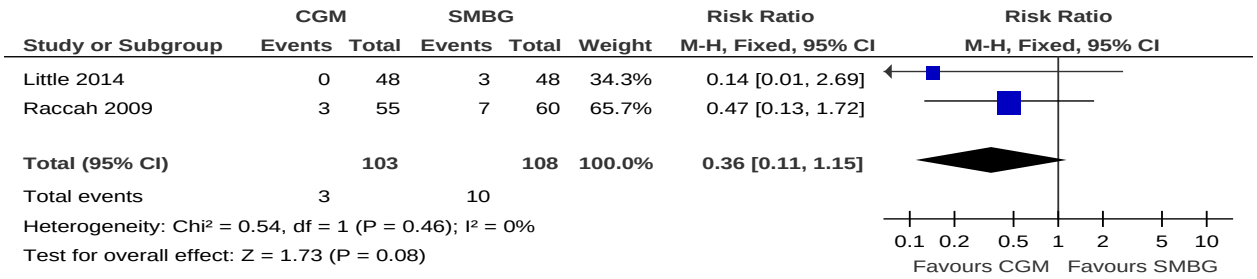


Figure 73: Adverse events – follow-up less than or equal to 6 months



J.4 Insulin therapy

J.4.1 Rapid-acting insulin

J.4.1.1 Lispro versus Human insulin (less than or equal to 6 months and more than 6 months)

Figure 74: HbA1c (final value) – all studies

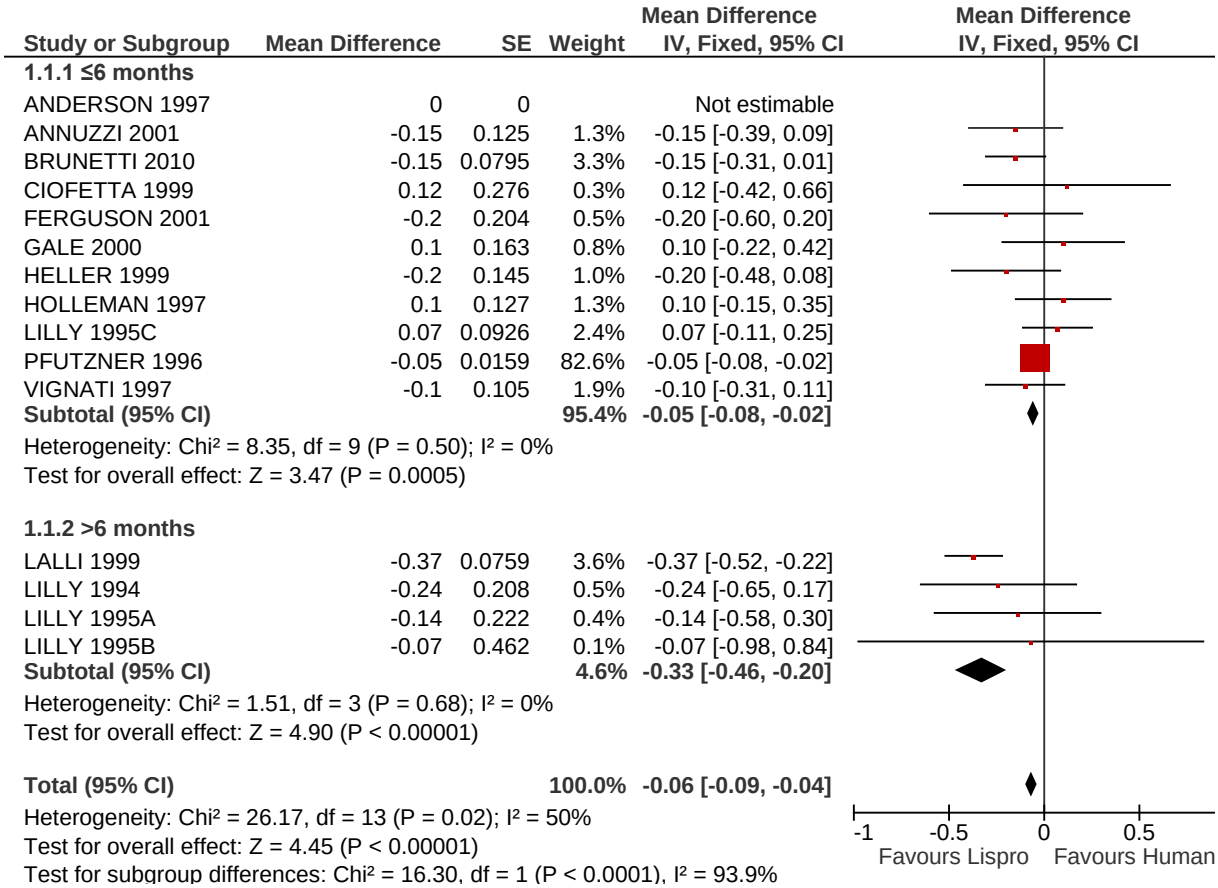


Figure 75: HbA1c (final value) – split by different basal NPH regimen (once/day and twice/day)

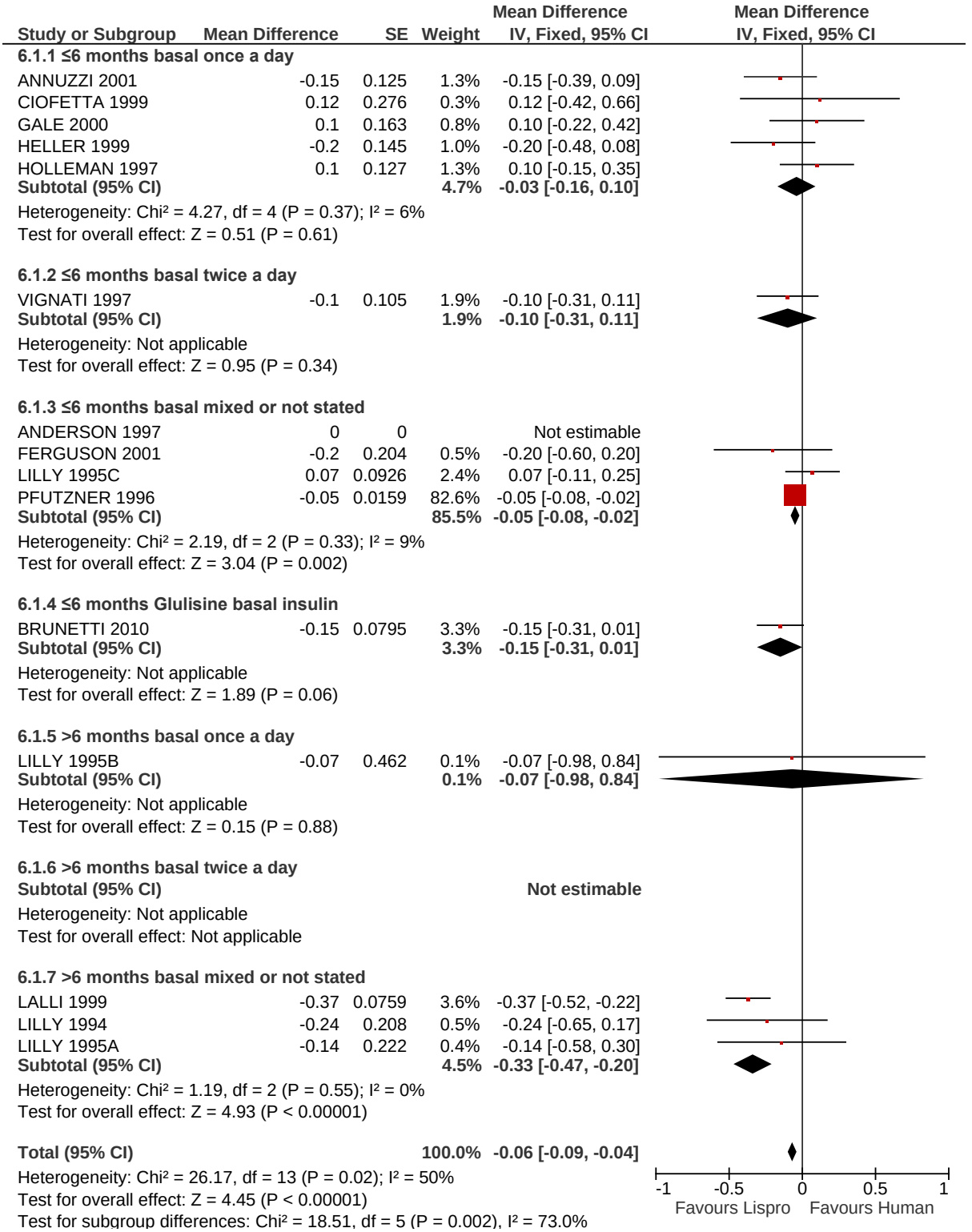


Figure 76: Severe/major hypoglycaemia (no. of patients) – all studies

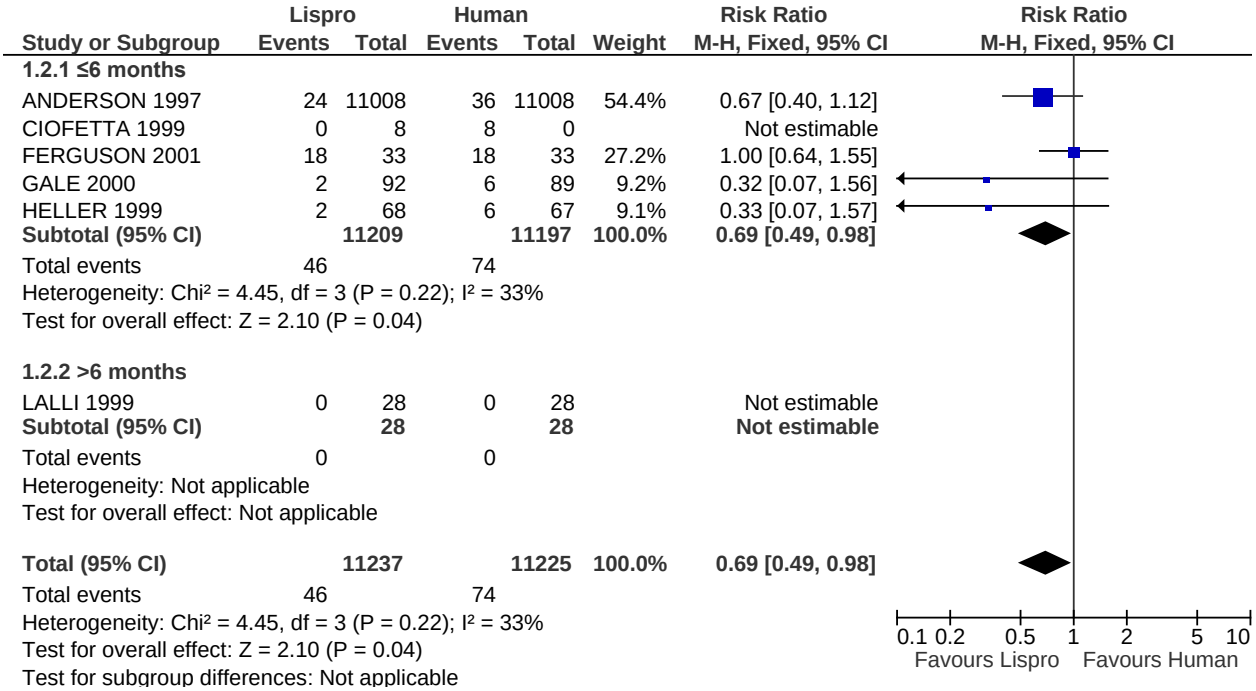


Figure 77: Severe/major hypoglycaemia (no. of patients) – split by different basal NPH regimen (once/day and twice/day)

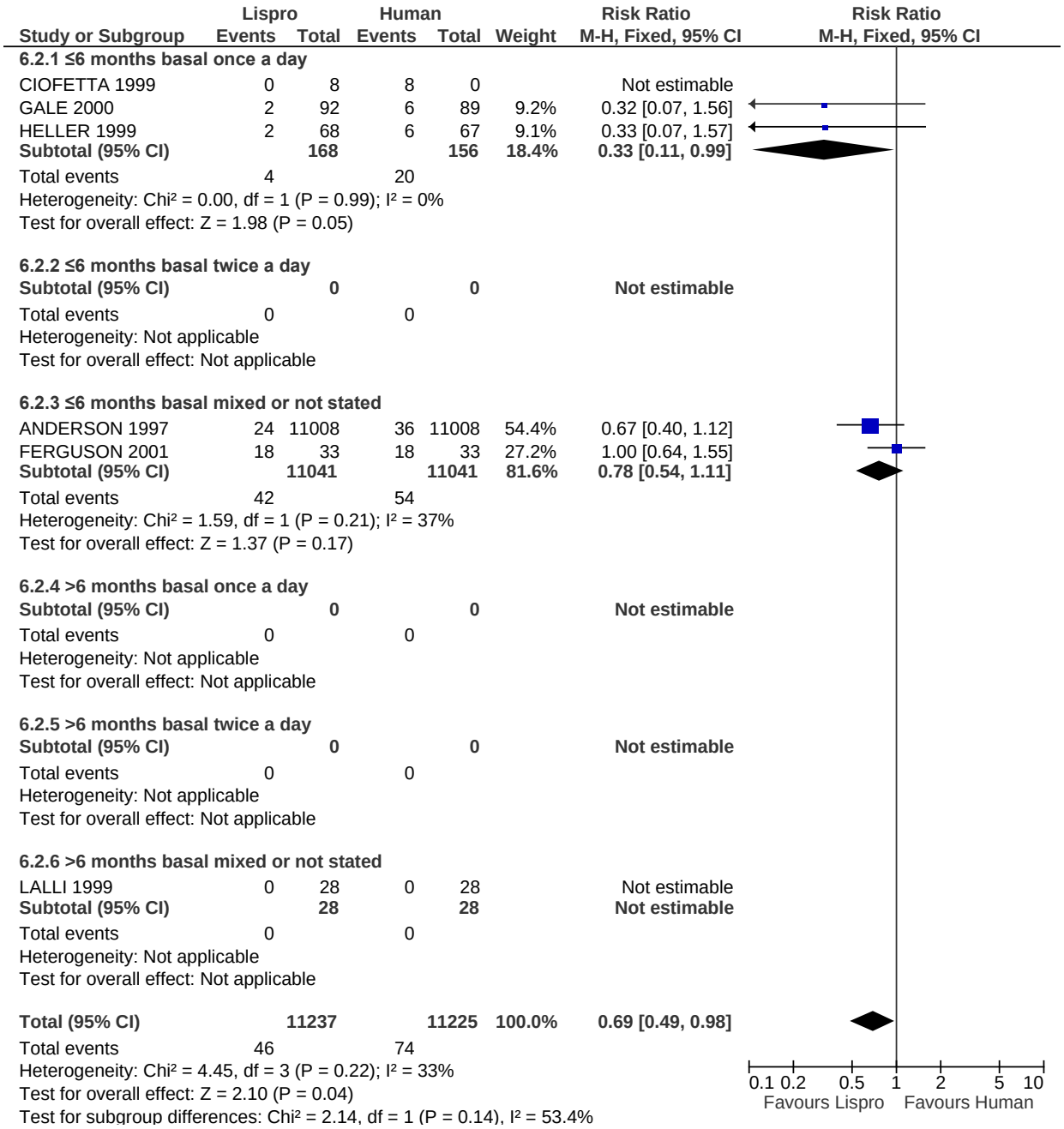


Figure 78: Severe hypoglycaemia (episodes) – all studies

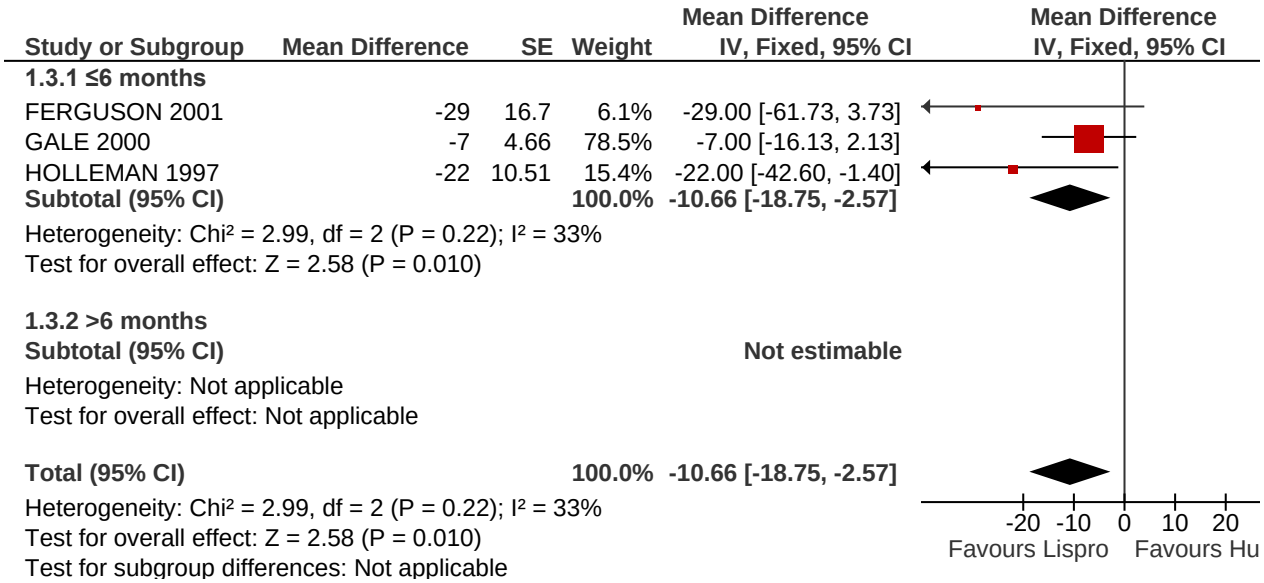


Figure 79: Severe hypoglycaemia (episodes) – split by different basal NPH regimen (once/day and twice/day)

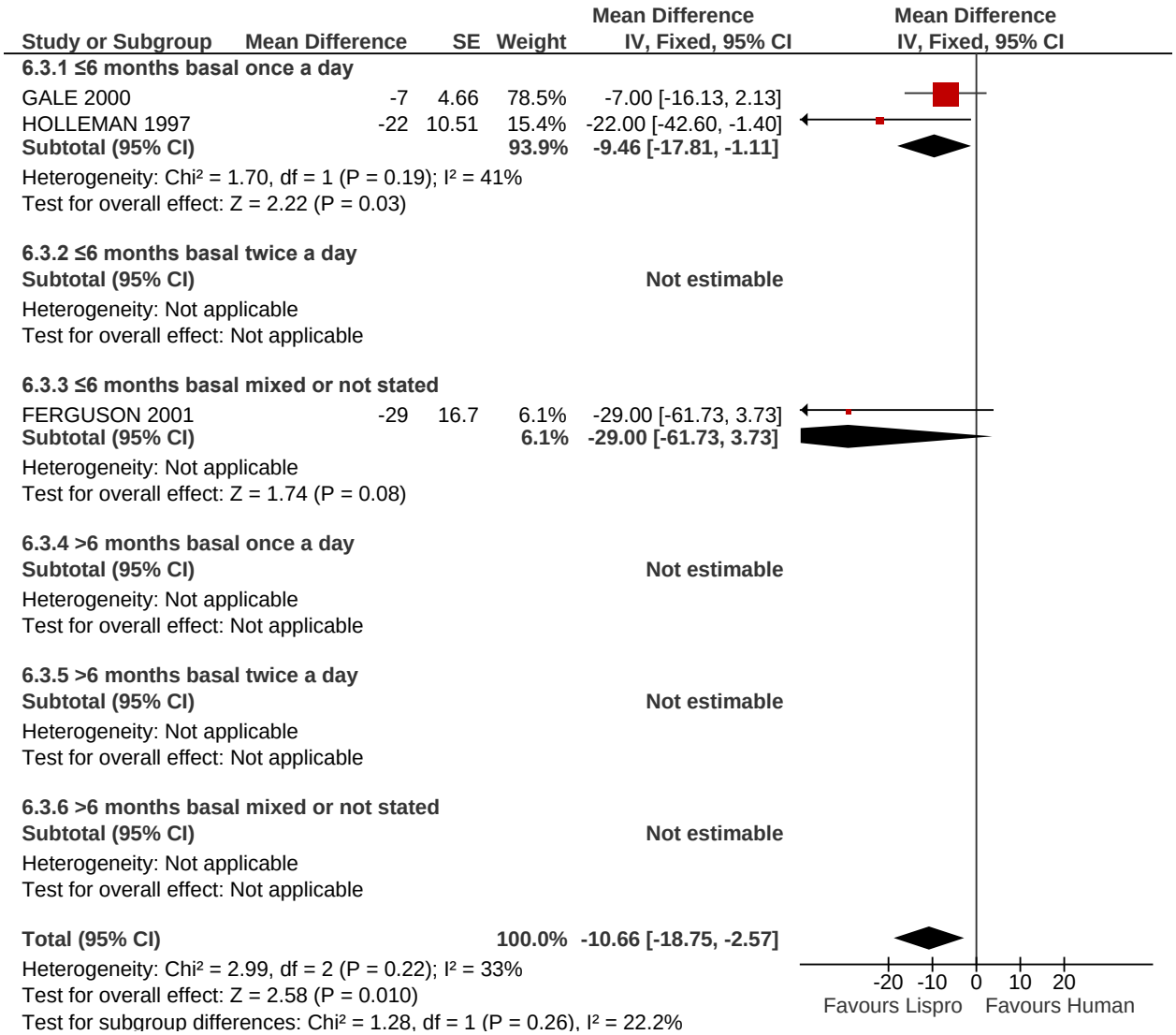


Figure 80: Hypoglycaemia/minor hypoglycaemia (no. of patients)

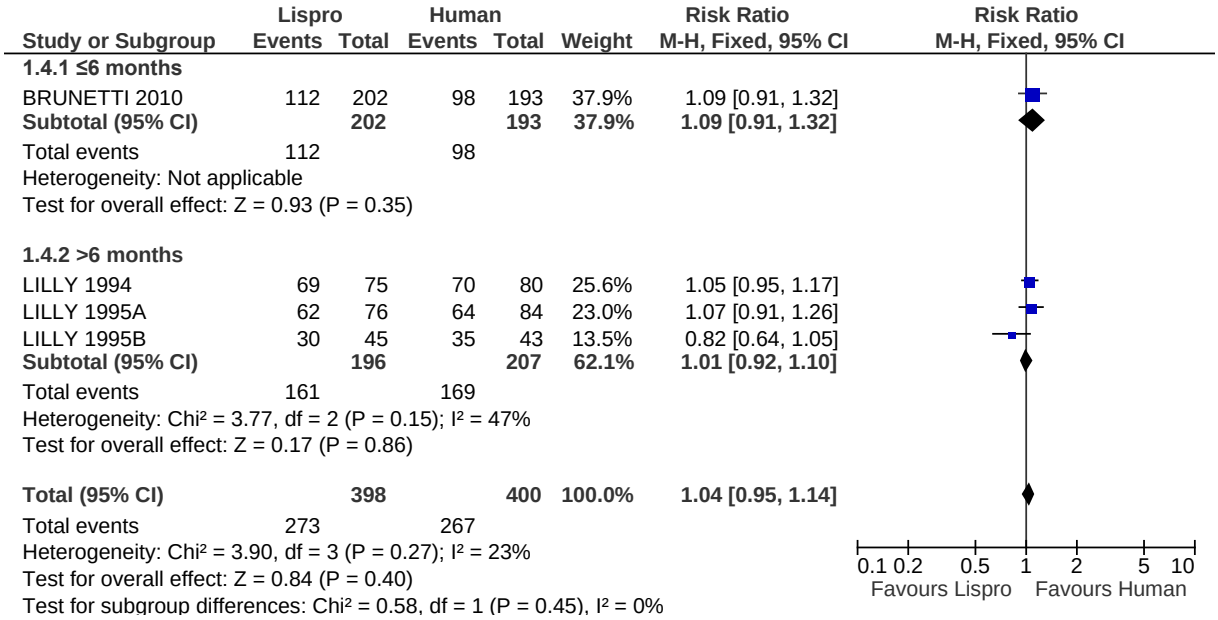


Figure 81: Hypoglycaemia (episodes)

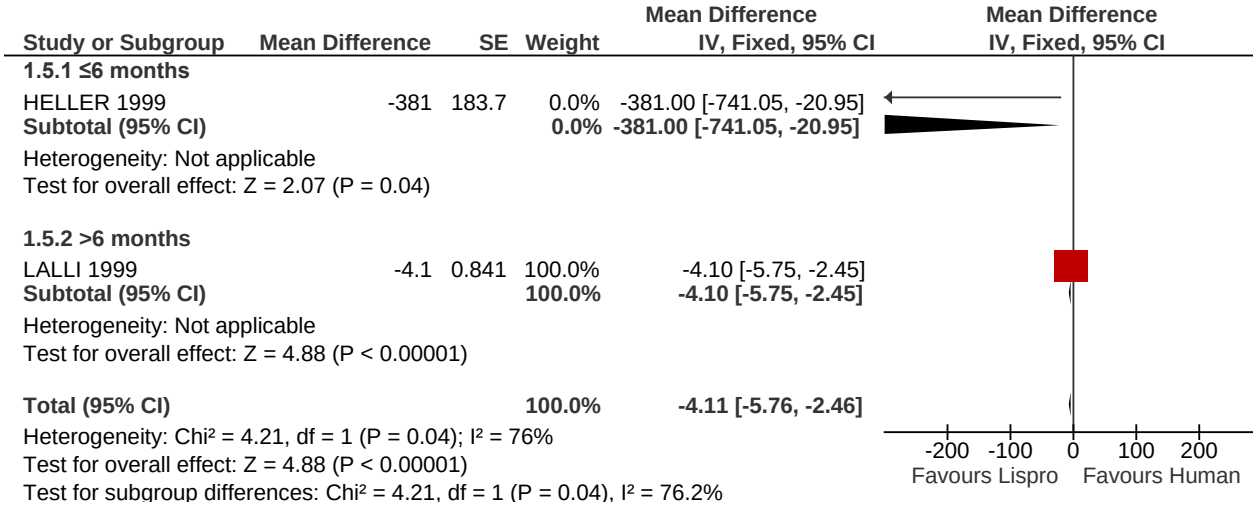


Figure 82: Hypoglycaemia (episodes/month)

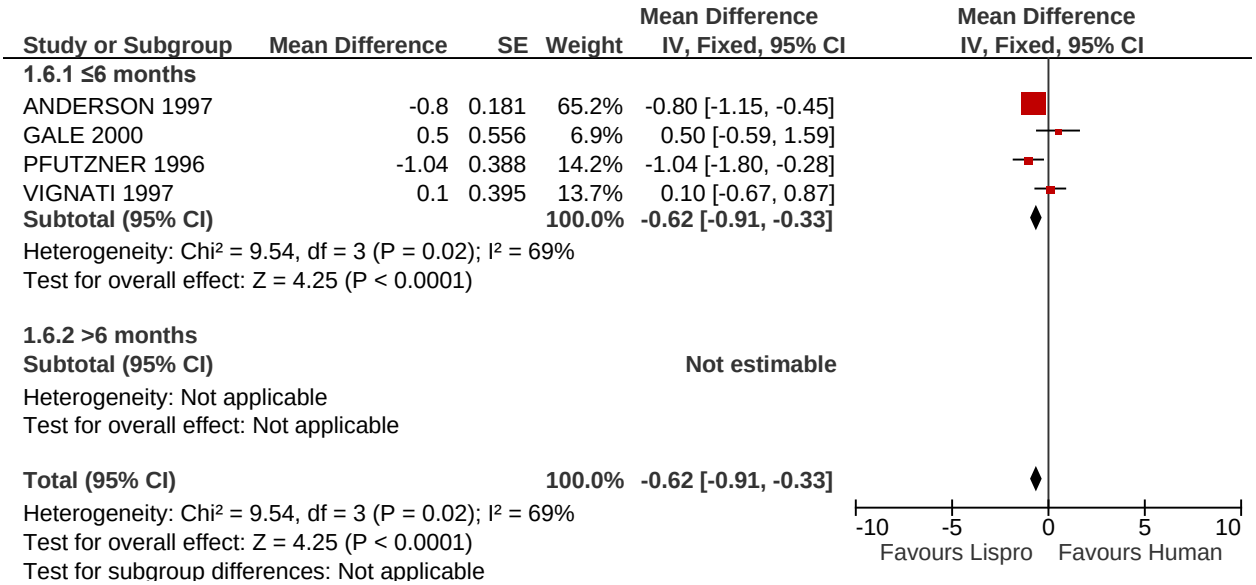


Figure 83: Hypoglycaemia/mild hypoglycaemia (episodes/patient/month)

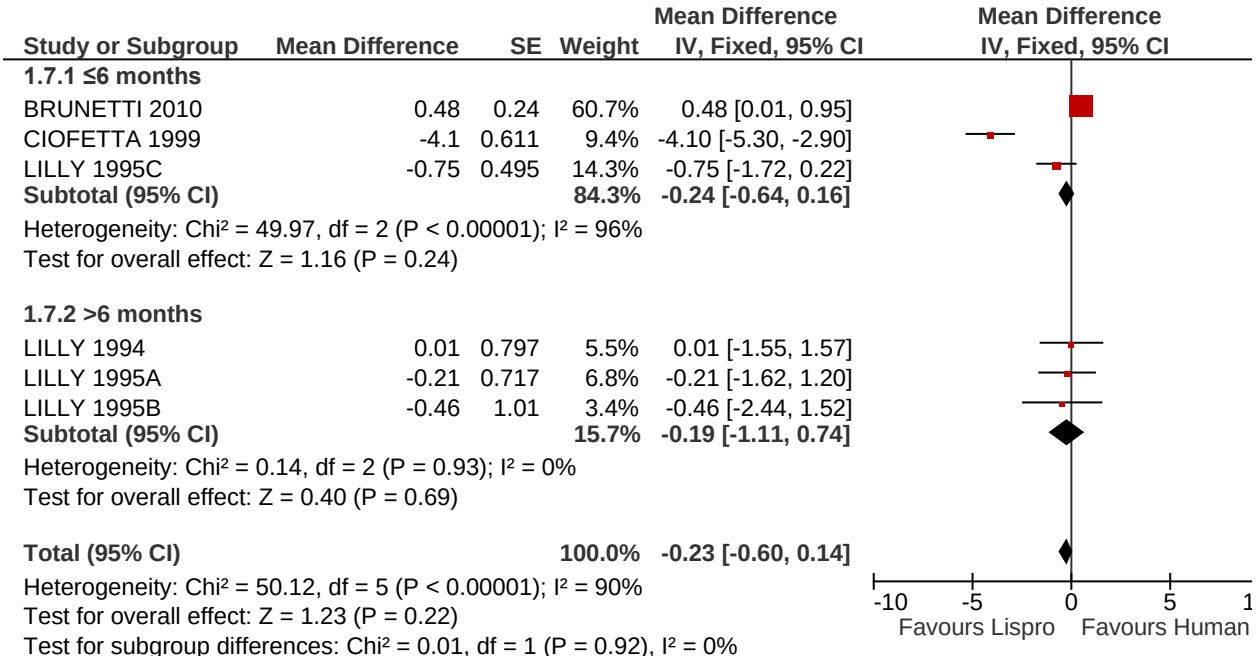


Figure 84: Nocturnal hypoglycaemia (episodes)

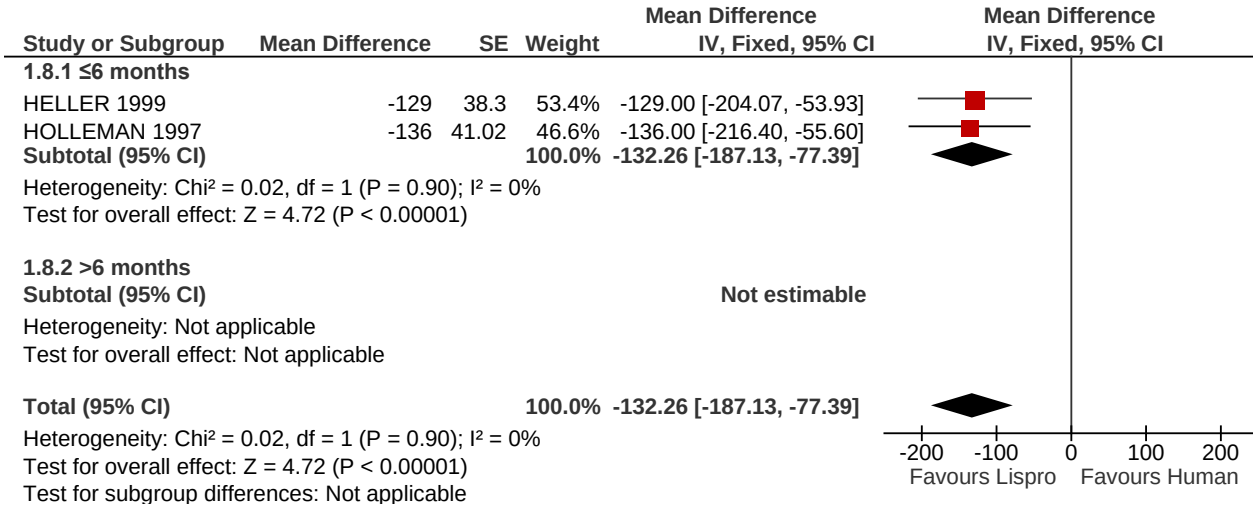


Figure 85: Nocturnal hypoglycaemia (episodes/month)

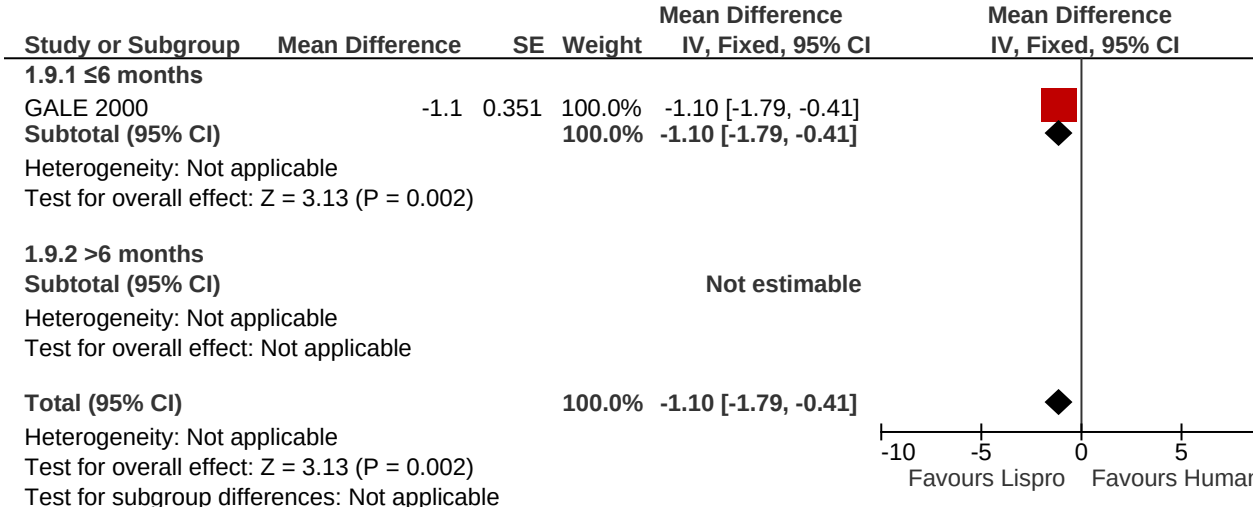


Figure 86: Weight, kg (final value)

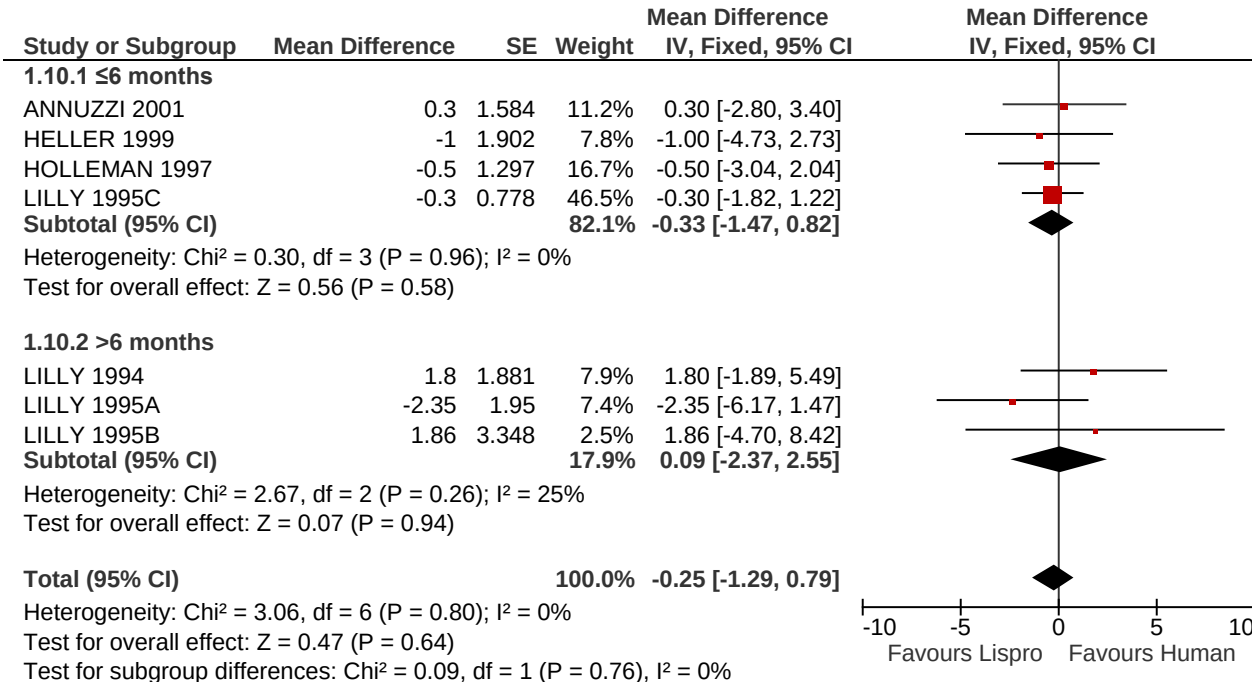
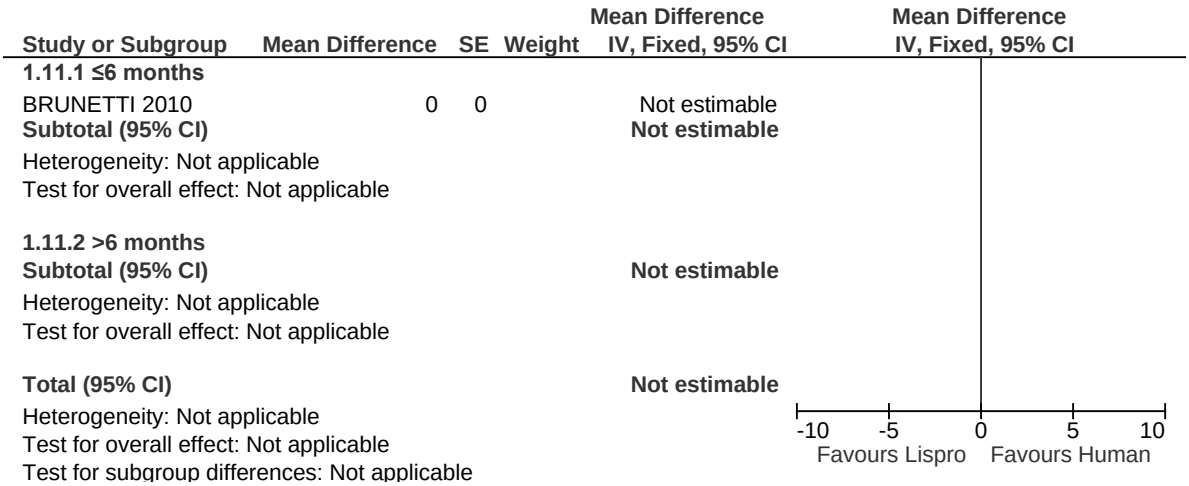


Figure 87: QoL (WED score)



J.4.1.2 Lispro versus Glulisine (less than or equal to 6 months and more than 6 months)

Figure 88: HbA1c (final value) – all studies

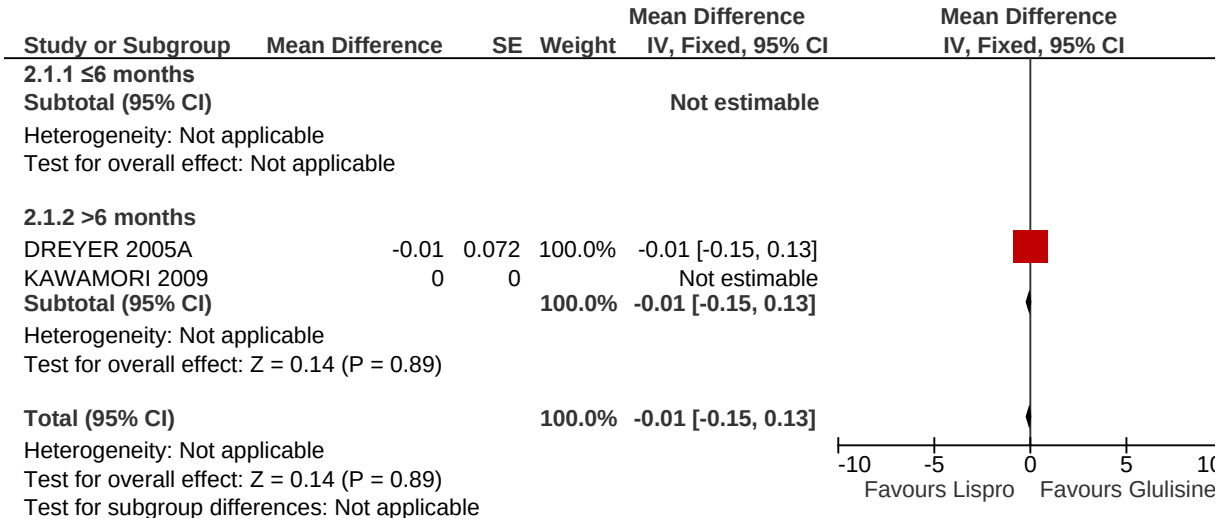


Figure 89: Hypoglycaemia (episodes/patient-month)

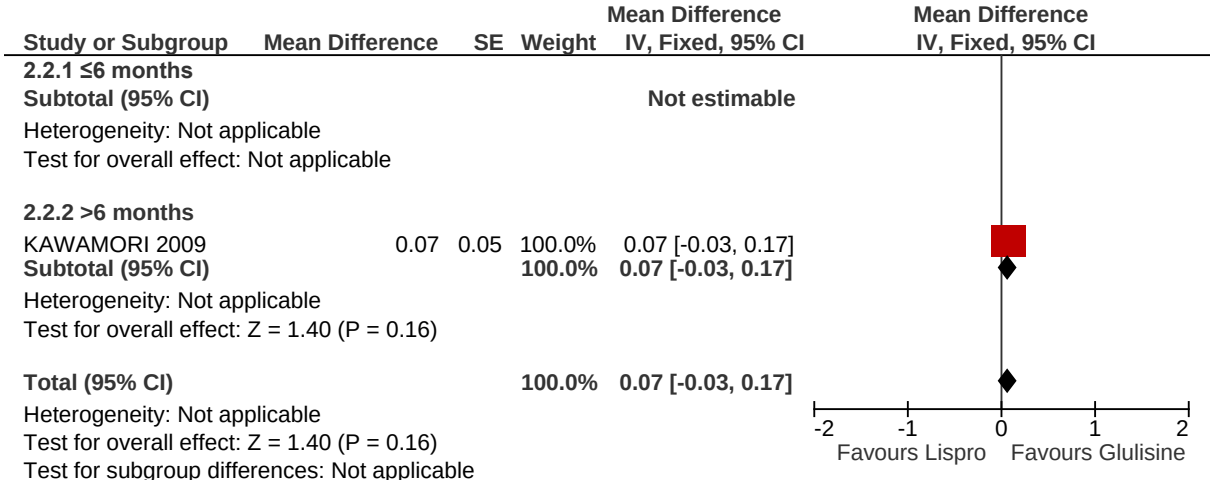


Figure 90: Hypoglycaemia (episodes/patient-months)

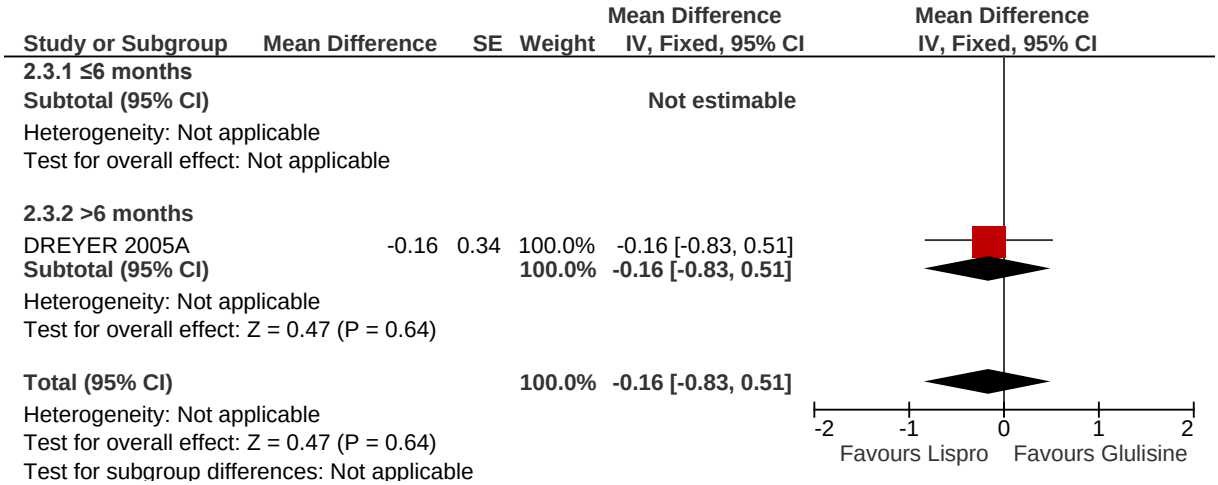


Figure 91: Severe hypoglycaemia (episodes/patient-month)

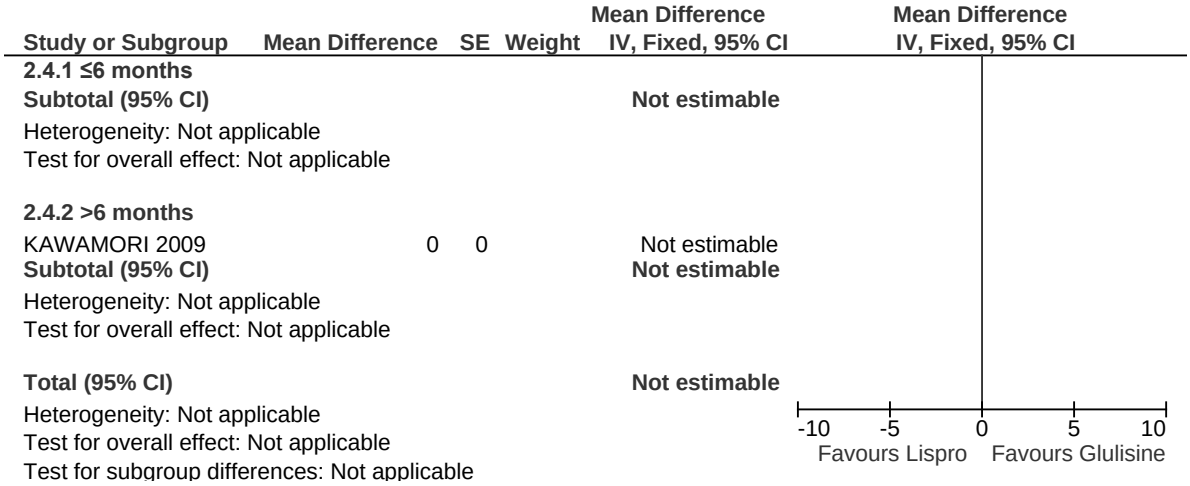


Figure 92: Severe hypoglycaemia (episodes/patient-months)

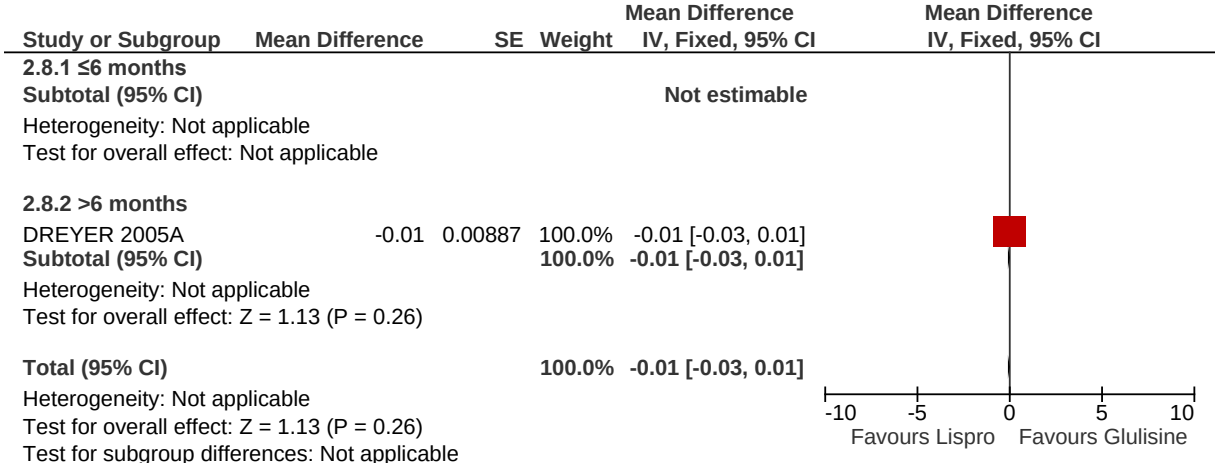


Figure 93: Nocturnal hypoglycaemia (episodes/patient-months)

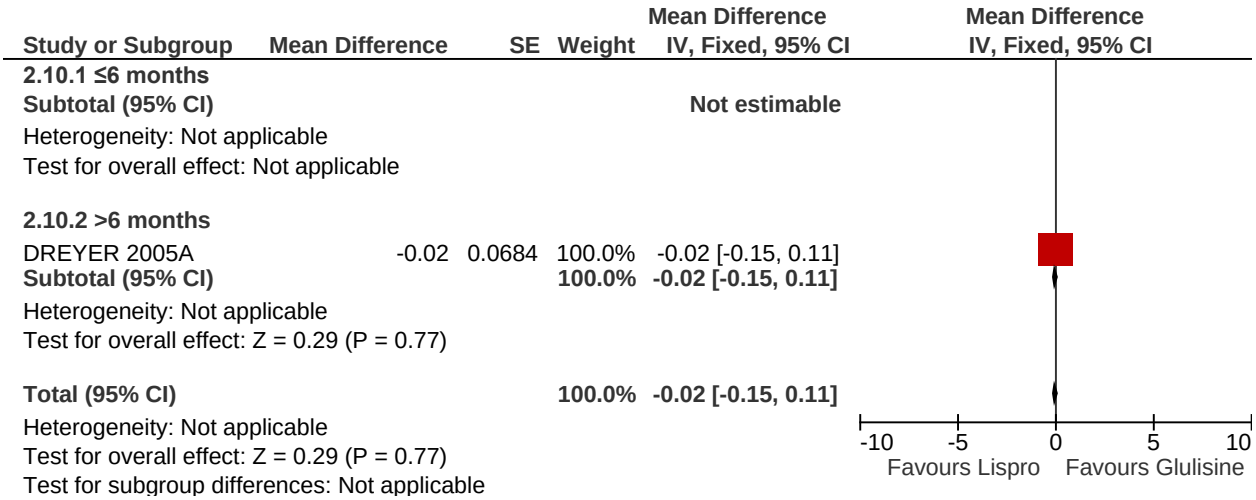
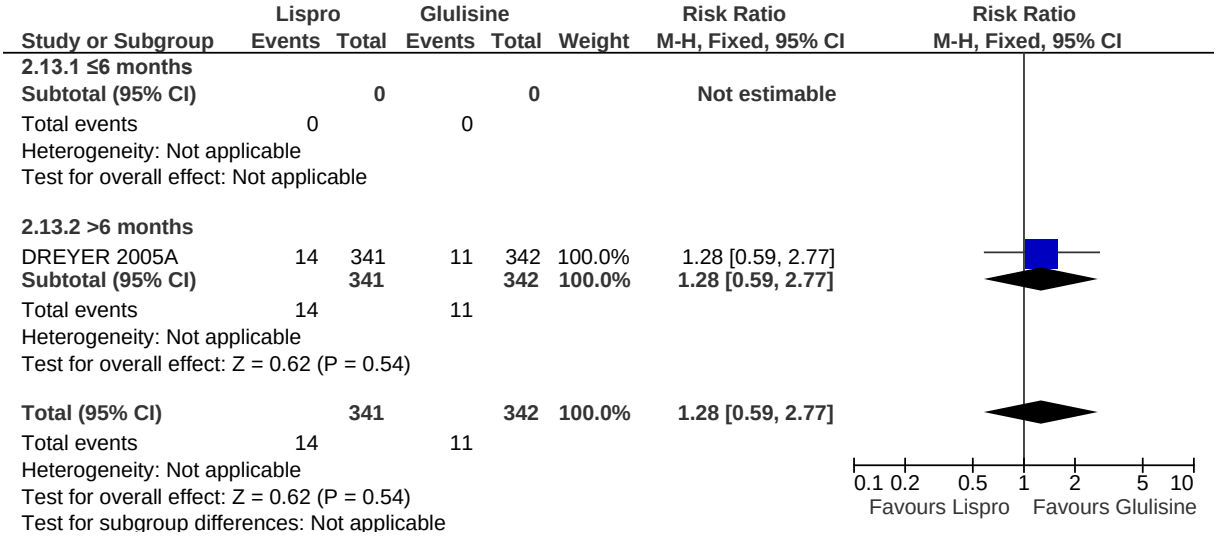


Figure 94: Injection site reactions (no. of patients)



J.4.1.3 Aspart versus human insulin (less than or equal to 6 months and more than 6 months)

Figure 95: HbA1c (final value) – all studies

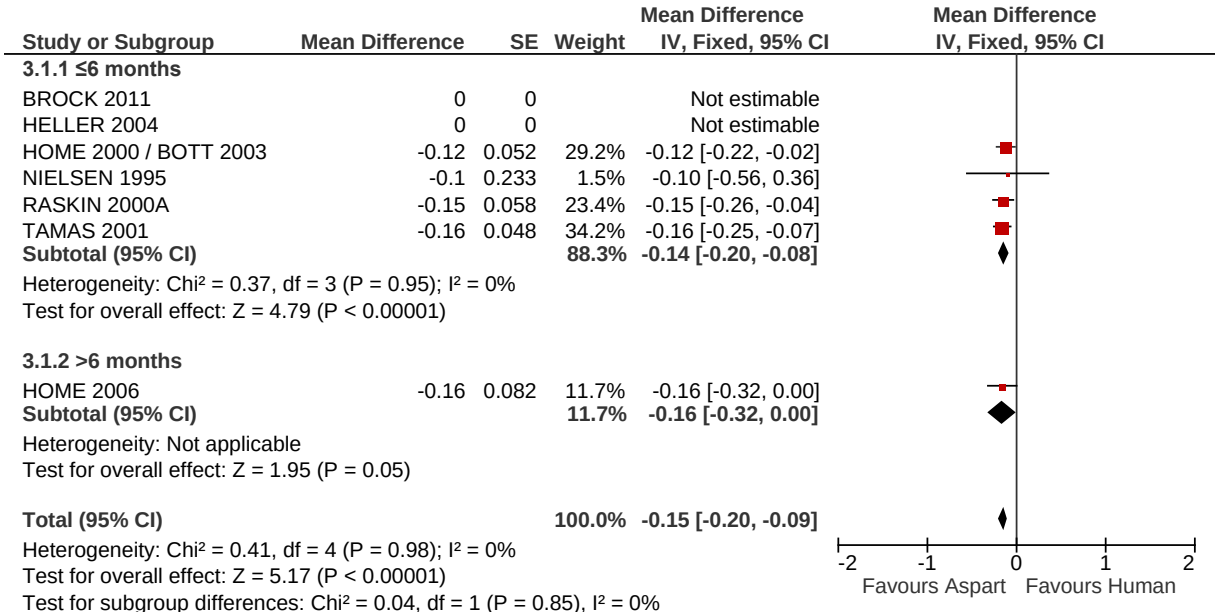


Figure 96: HbA1c (final value) - split by different basal NPH regimen (once/day and twice/day)

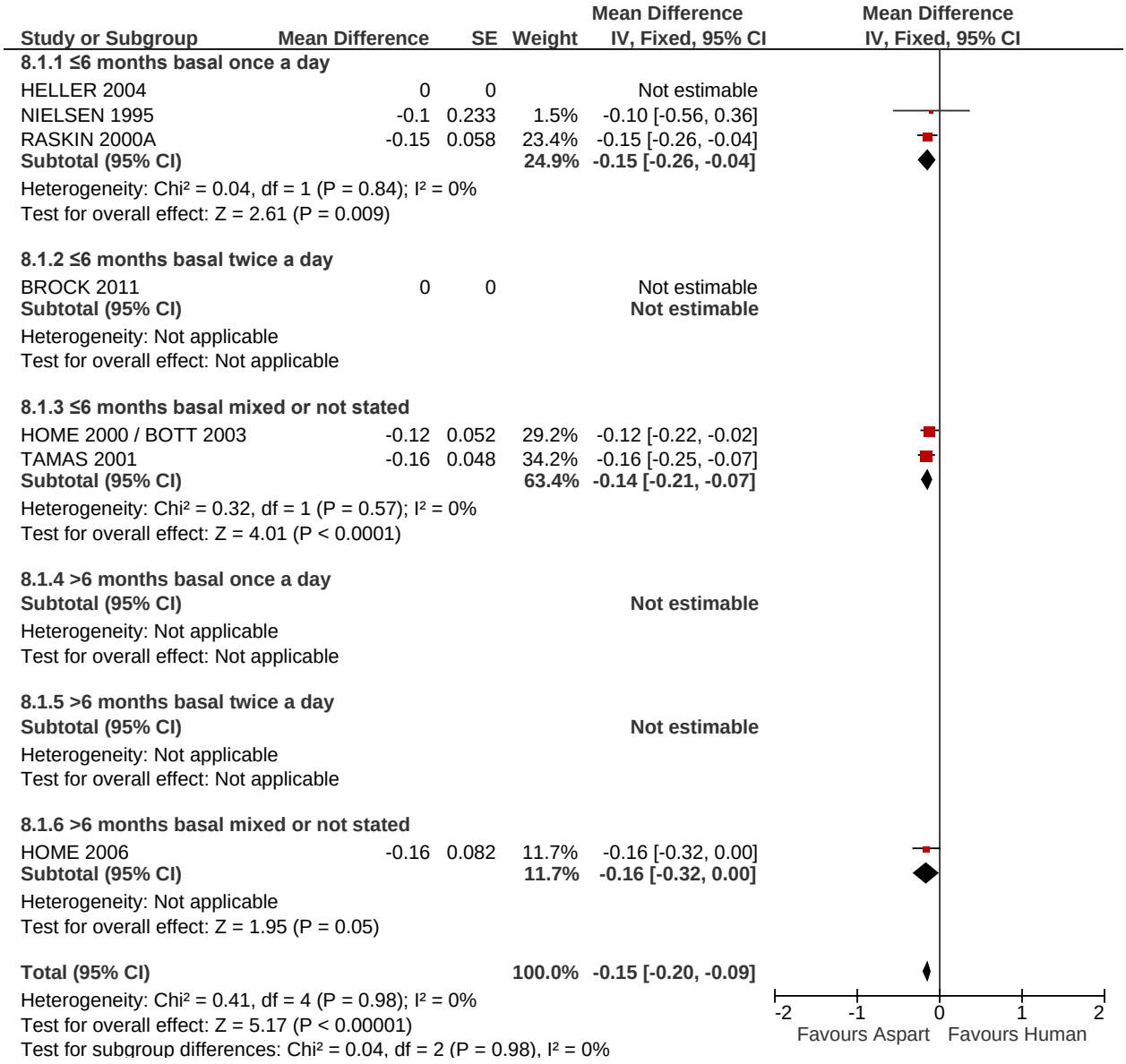


Figure 97: Severe/major hypoglycaemia (no. of patients) – all studies

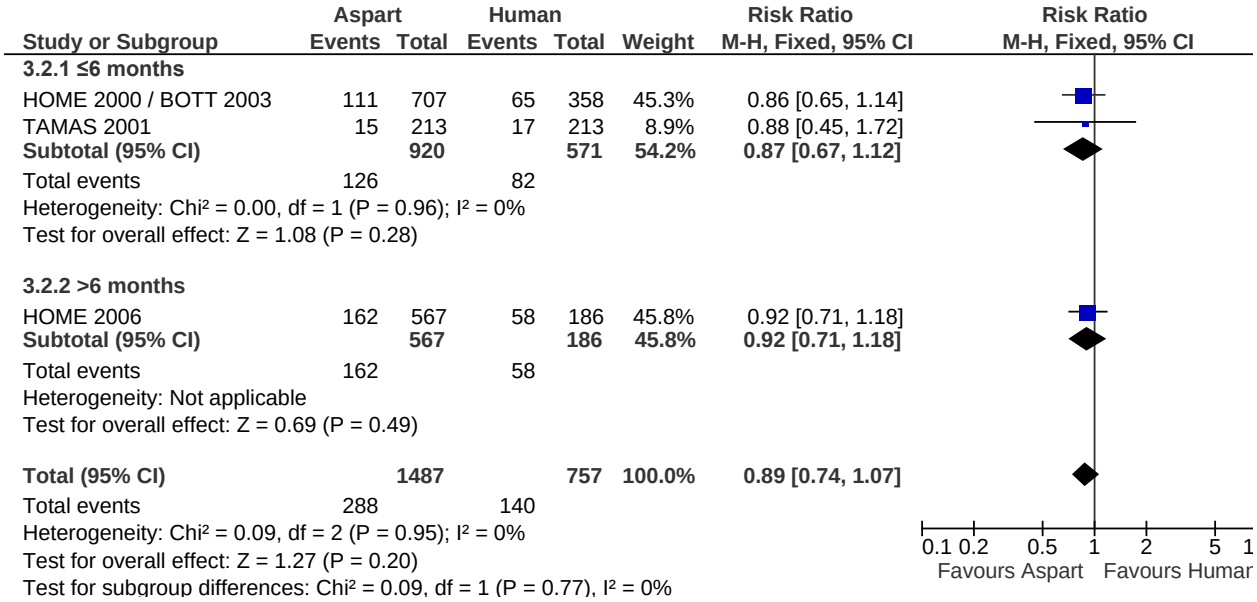


Figure 98: Severe/major hypoglycaemia (no. of patients) – split by different basal NPH regimen (once/day and twice/day)

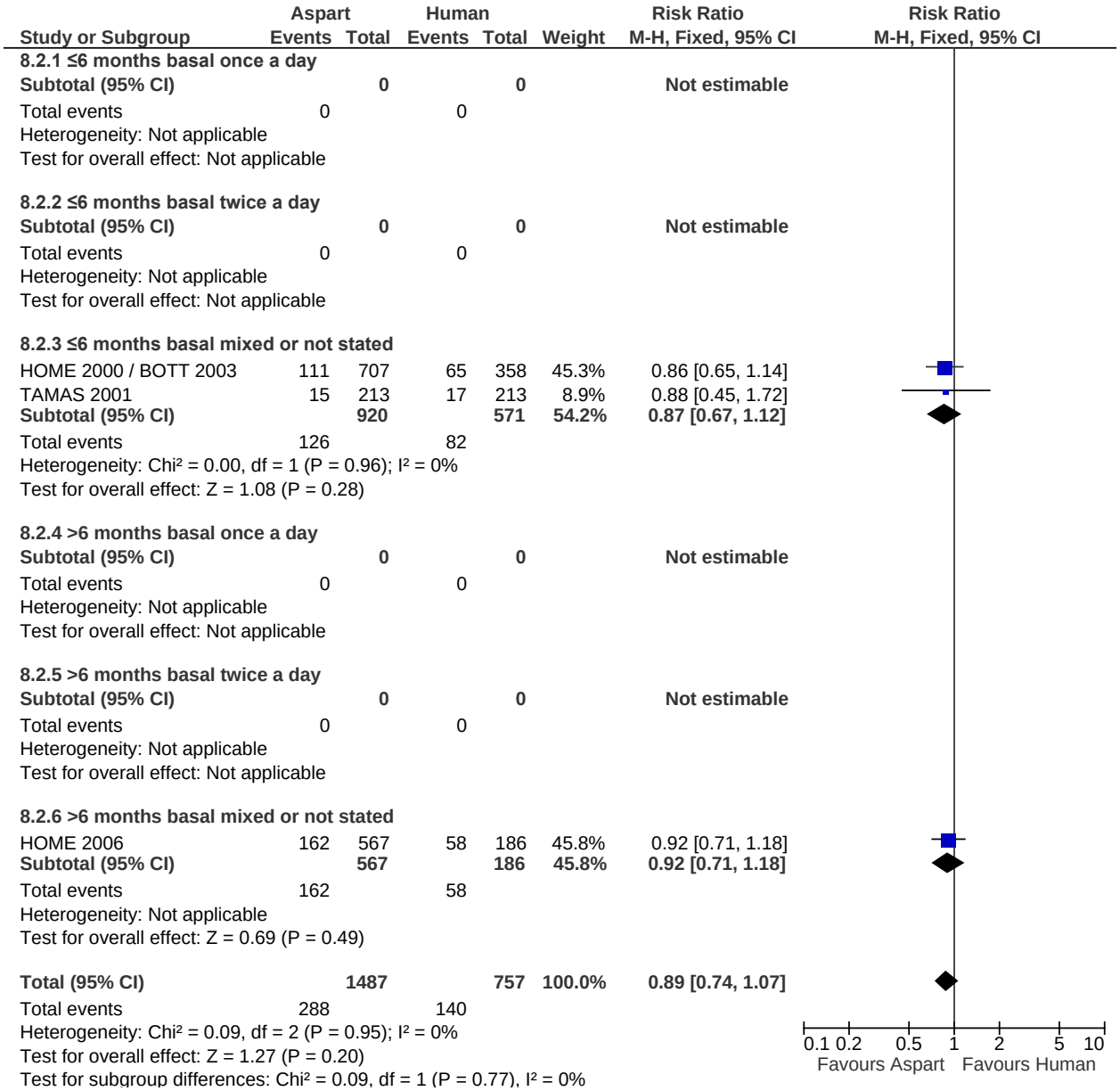


Figure 99: Hypoglycaemia/ minor hypoglycaemia (no. of patients)

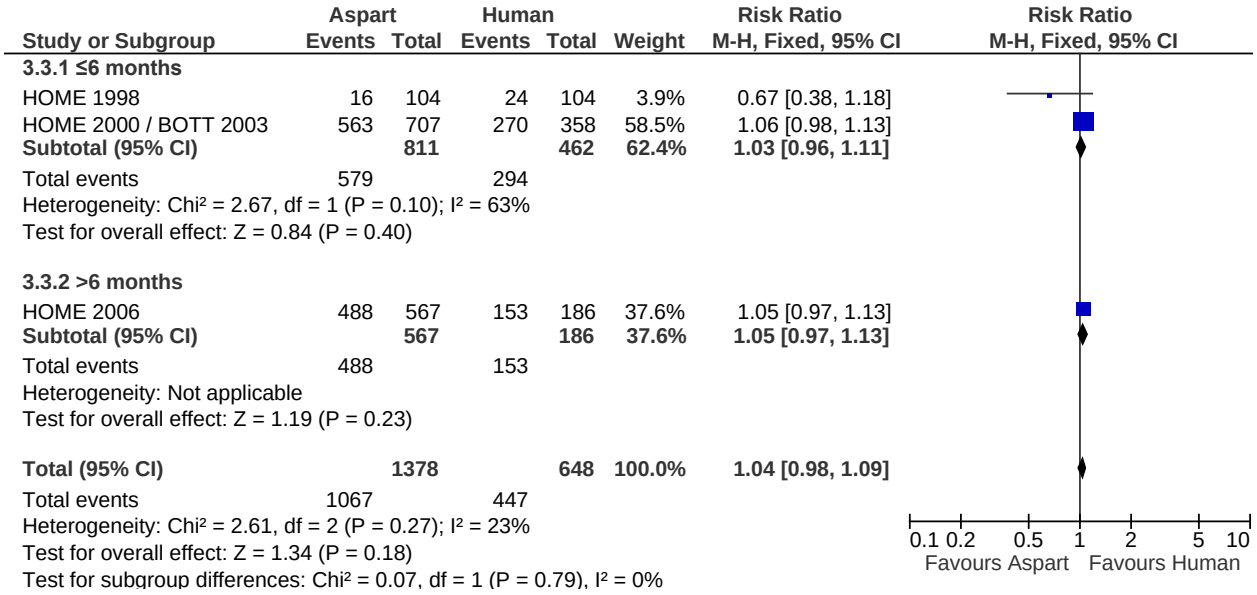


Figure 100: Hypoglycaemia (episodes/patient/week)

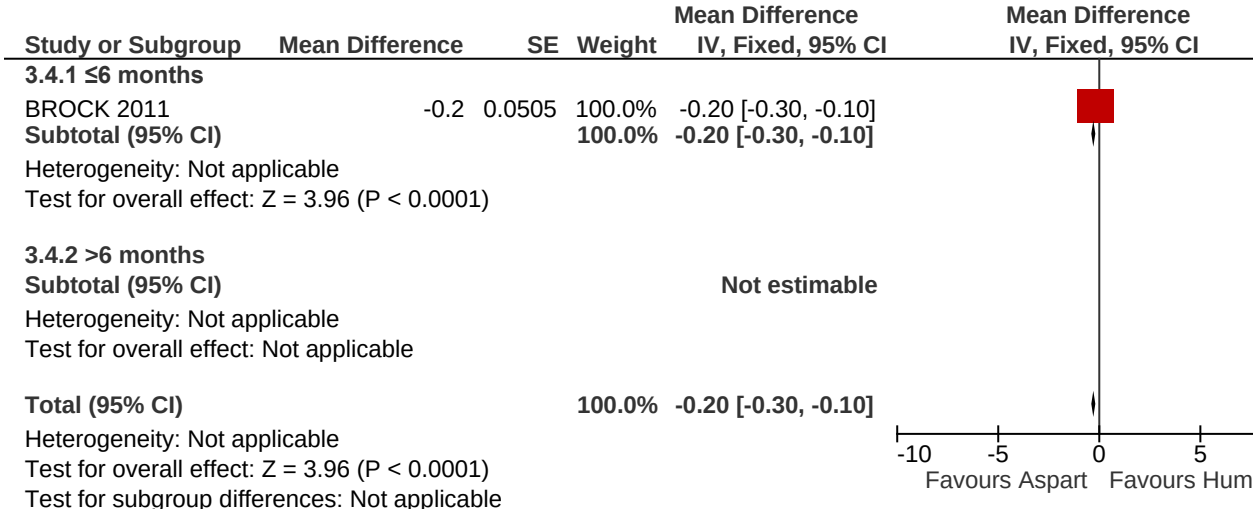


Figure 101: QoL – DTSQ (score 0-6)

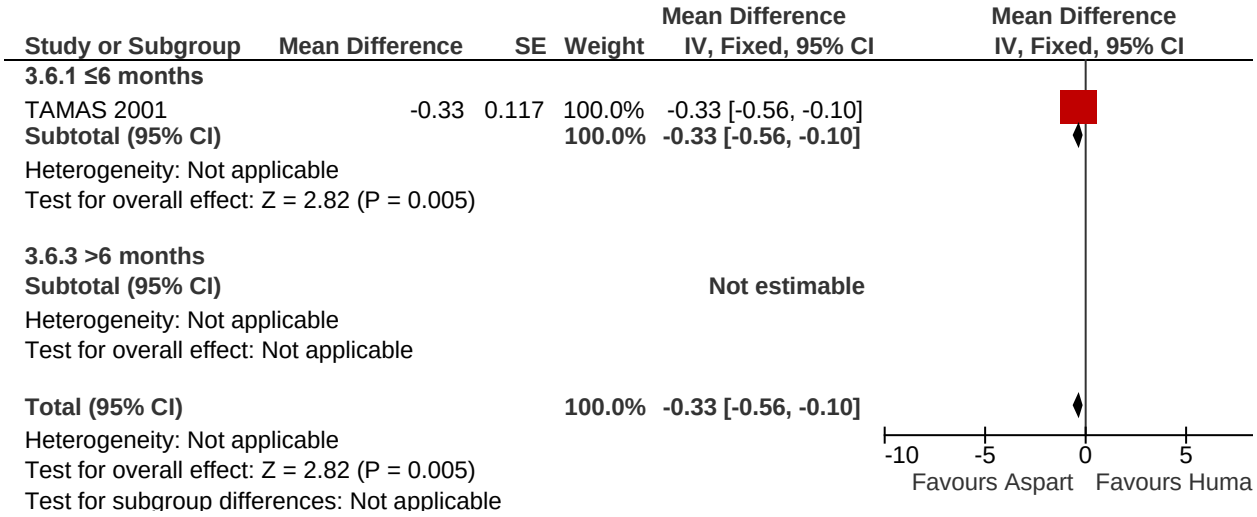
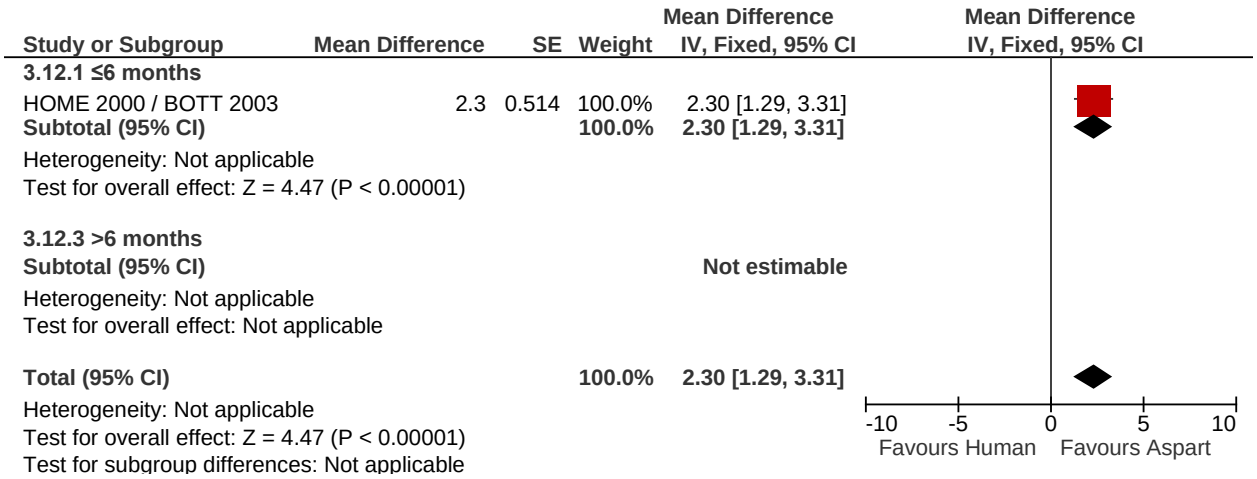


Figure 102: QoL – DTSQ (score 0-36)



J.4.1.4 Glulisine versus human insulin (less than or equal to 6 months and more than 6 months)

Figure 103: HbA1c (change score) less than 6 months

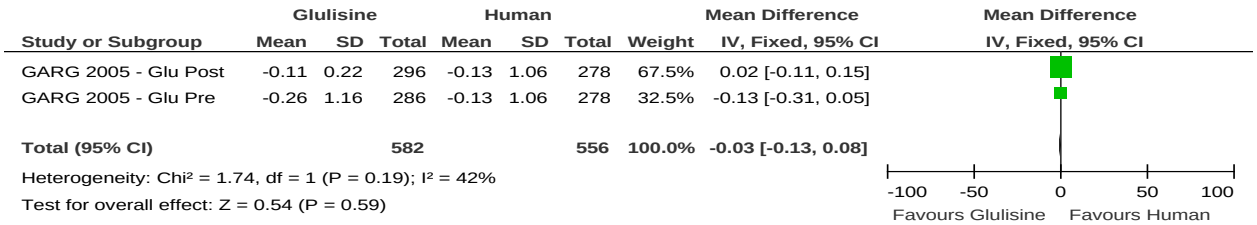


Figure 104: Severe/major hypoglycaemia (no. of patients)

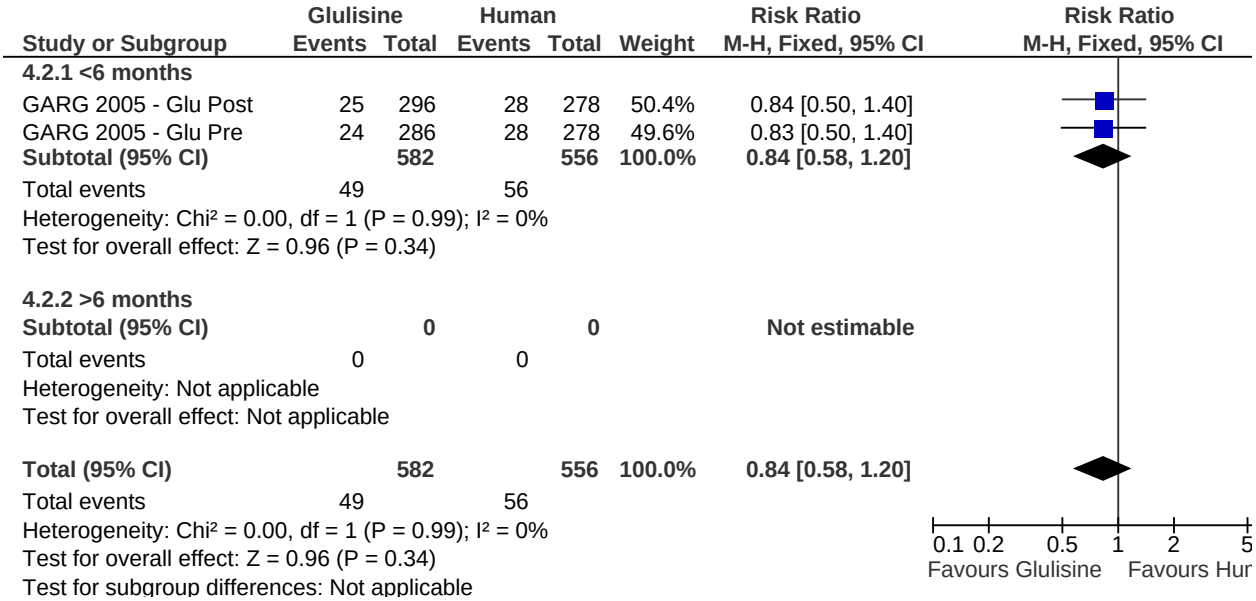


Figure 105: Severe hypoglycaemia (episodes/patient/month)

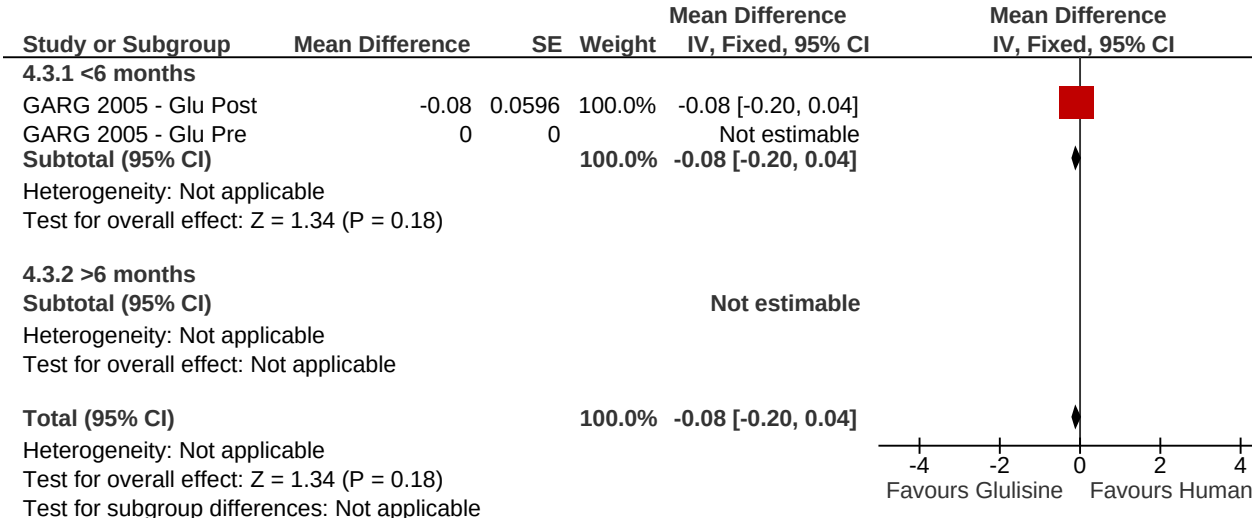


Figure 106: Hypoglycaemia/minor hypoglycaemia (no. of patients)

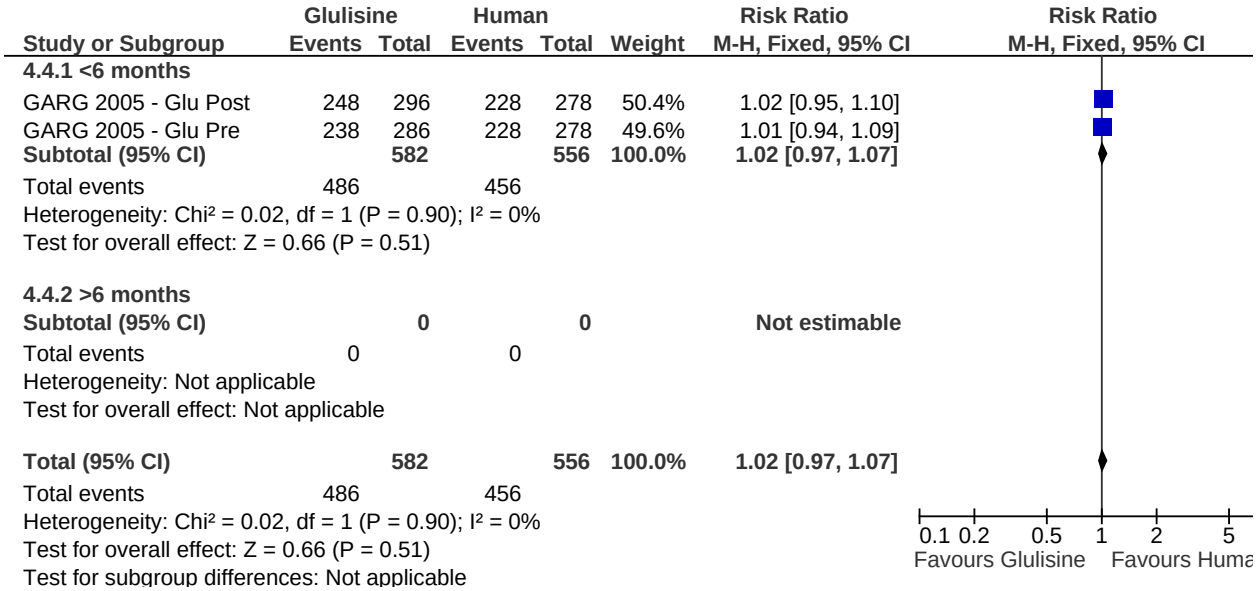


Figure 107: Hypoglycaemia (episodes/patient/month)

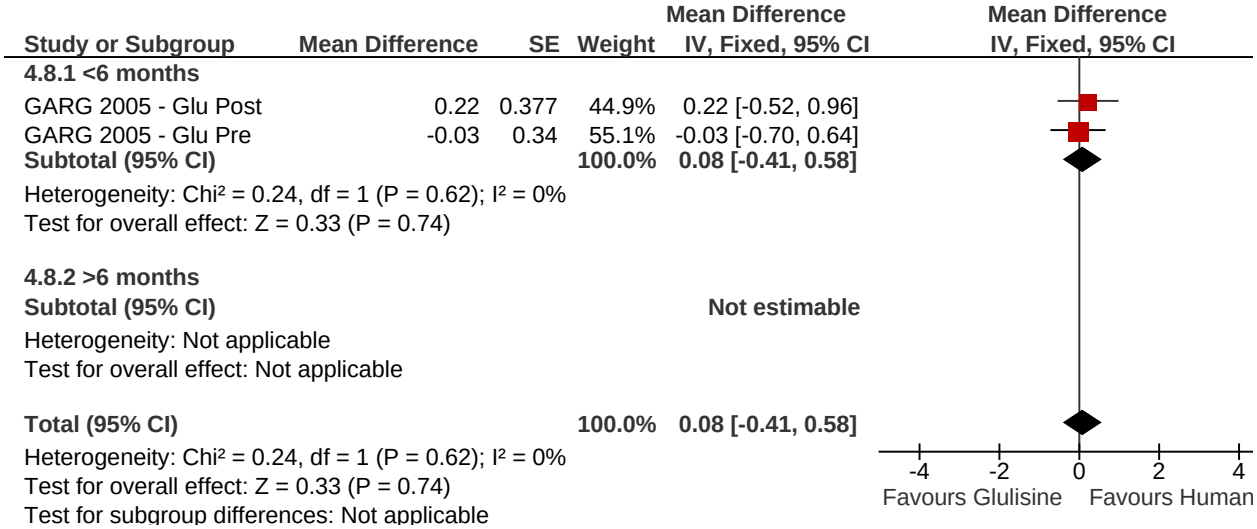


Figure 108: Nocturnal hypoglycaemia (no. of patients)

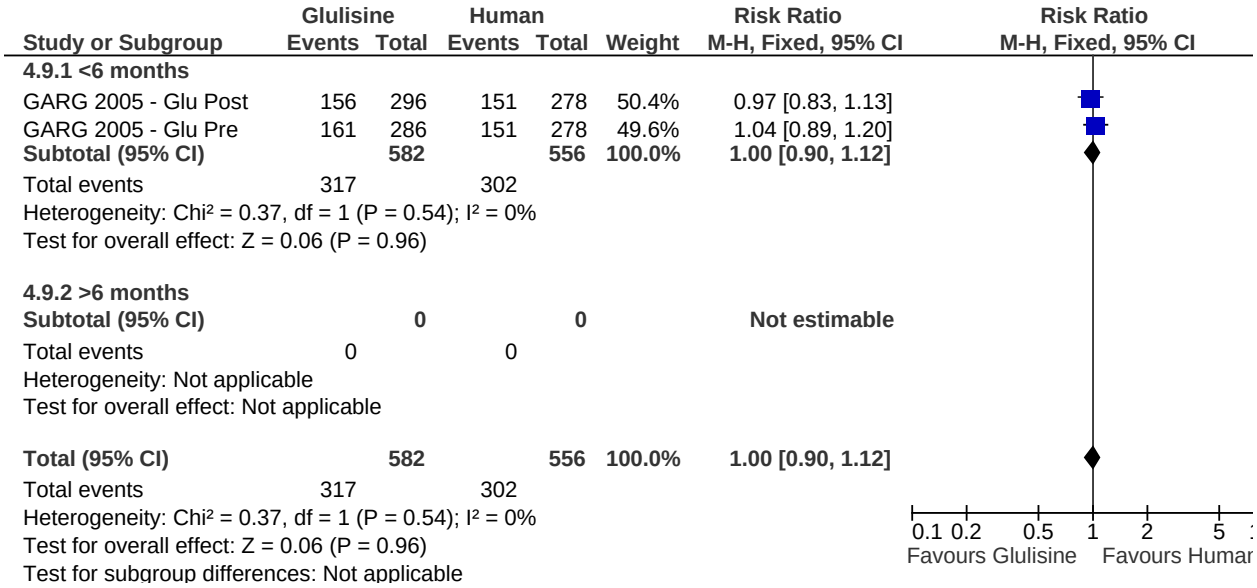
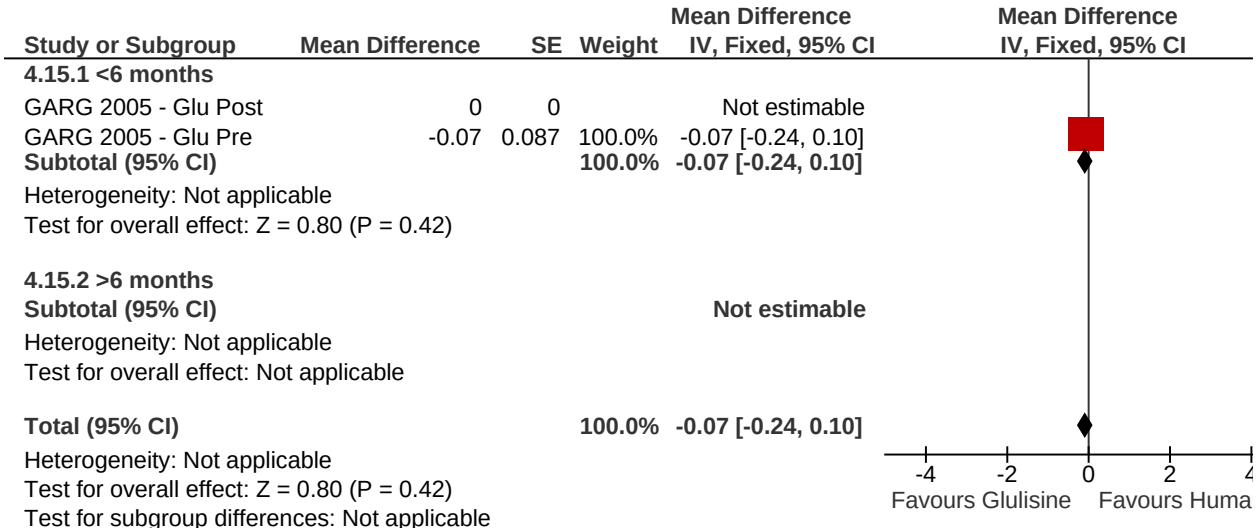


Figure 109: Nocturnal hypoglycaemia (episodes/patient/month)



J.4.2 Long-acting insulin

NOTE: Red arrows indicate studies that used regimens which reflect current clinical practice.

J.4.2.1 Degludec versus Glargine (less than or equal to 6 months and more than 6 months)

Figure 110: Reduction in HbA1c

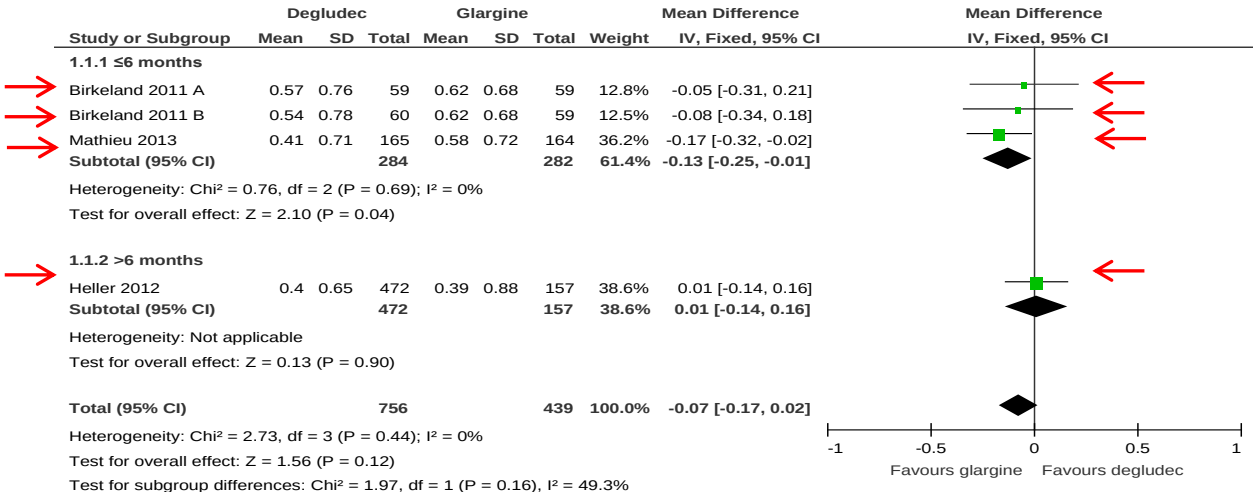


Figure 111: Body weight change

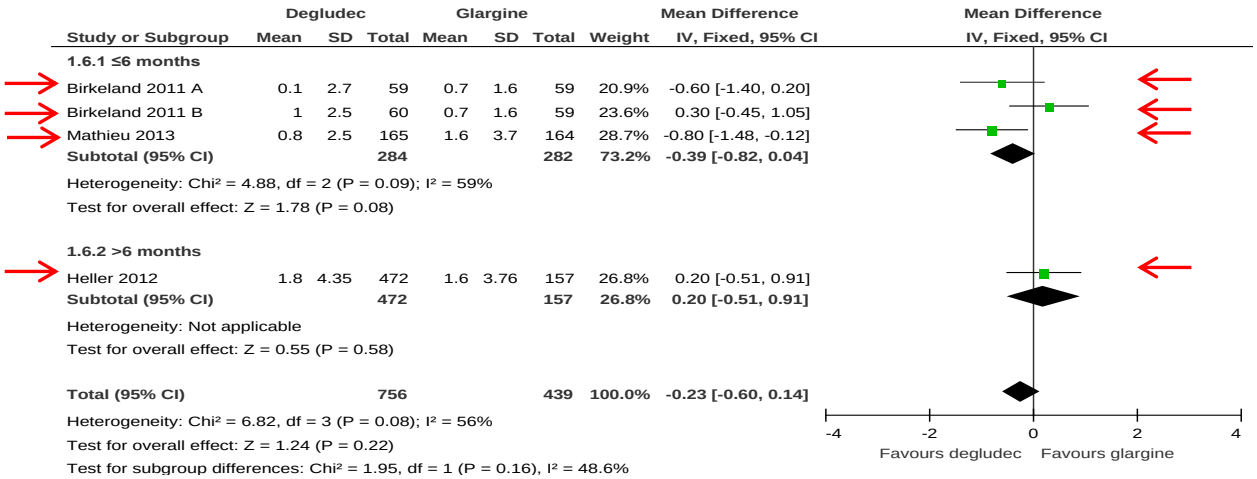


Figure 112: Severe hypoglycaemia

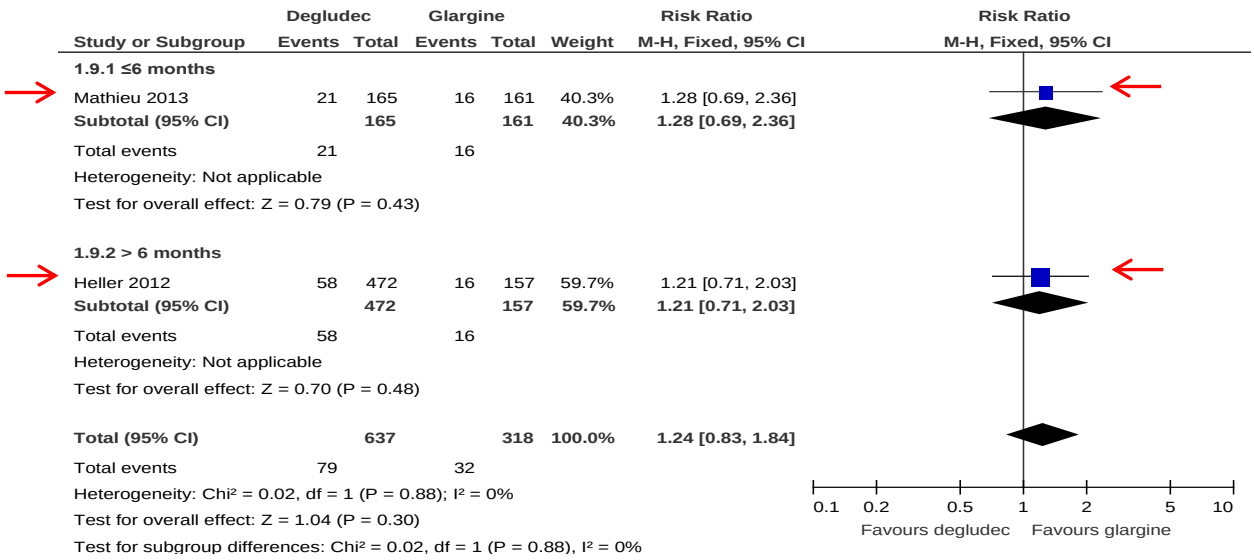


Figure 113: SF-36 physical component

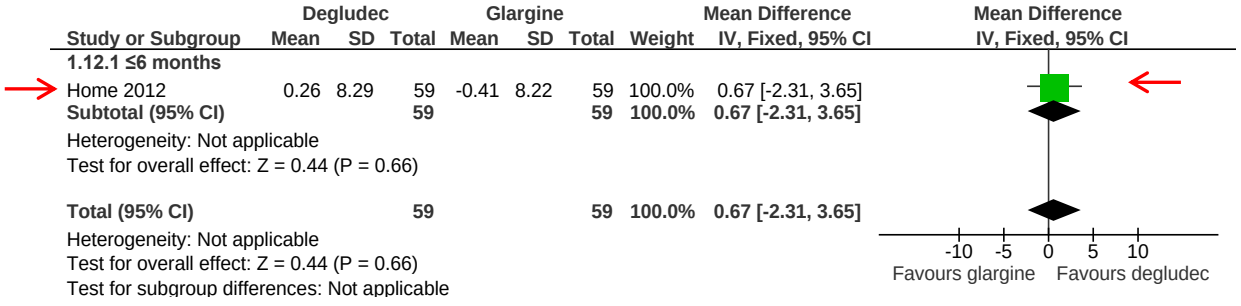


Figure 114: SF-36 mental component

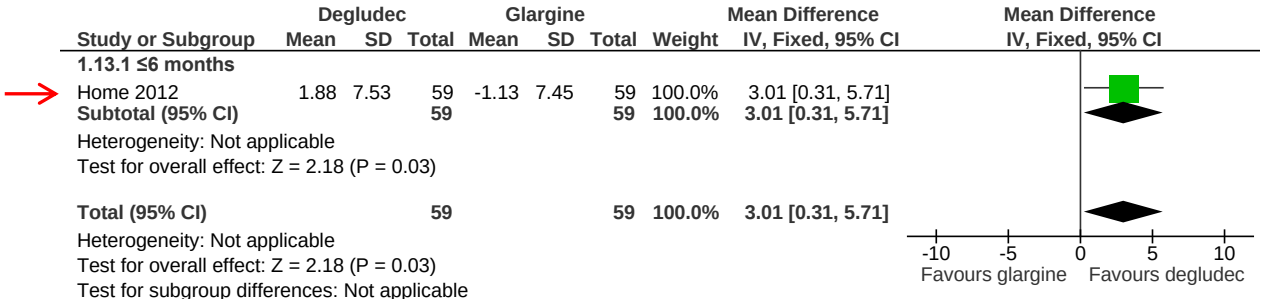


Figure 115: Severe adverse events

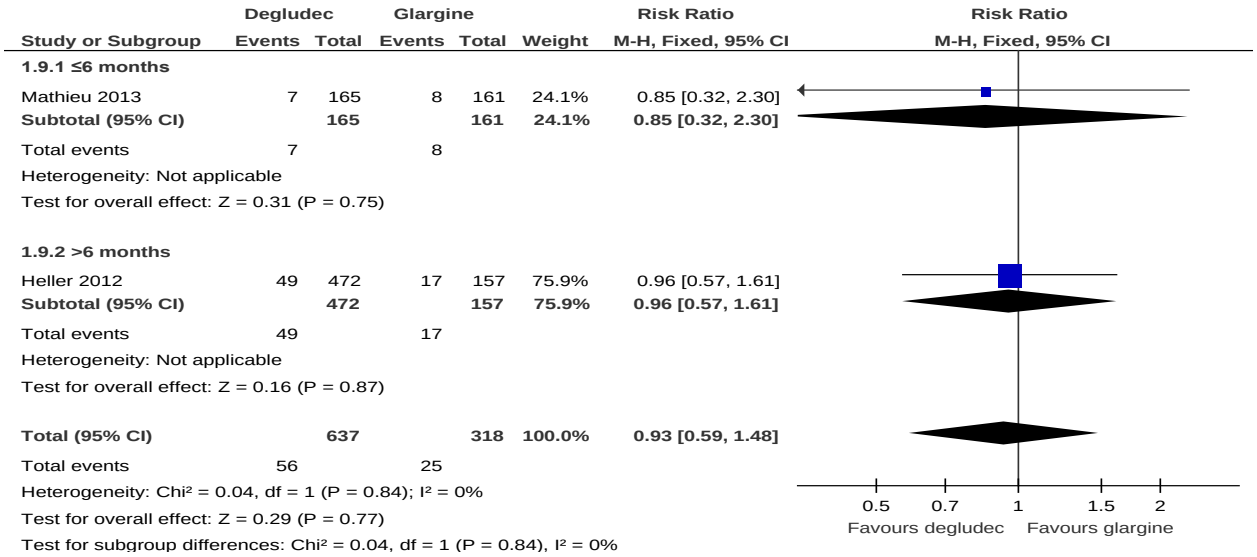
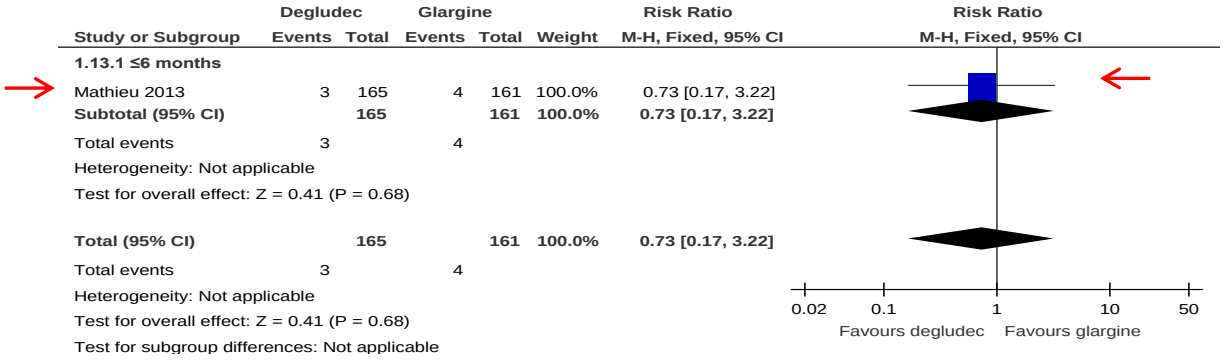


Figure 116: Injection site reactions



Source:

J.4.2.2 Detemir versus NPH (less than and equal to 6 months and more than 6 months)

Figure 117: HbA1c

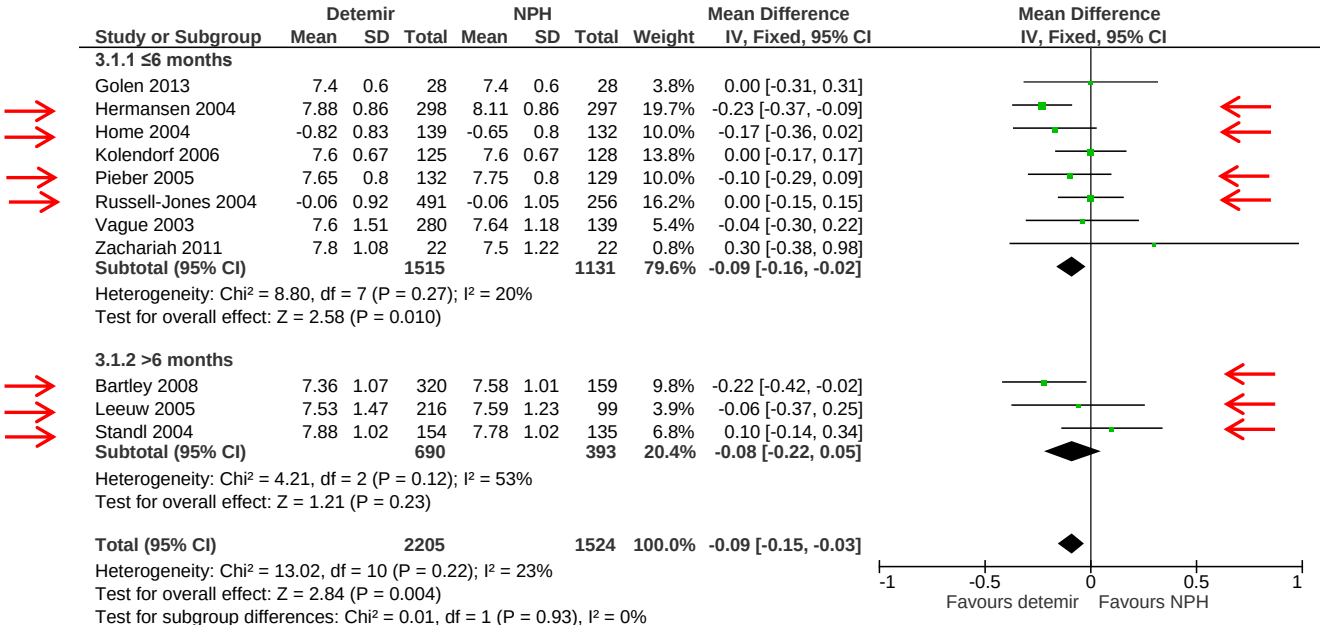
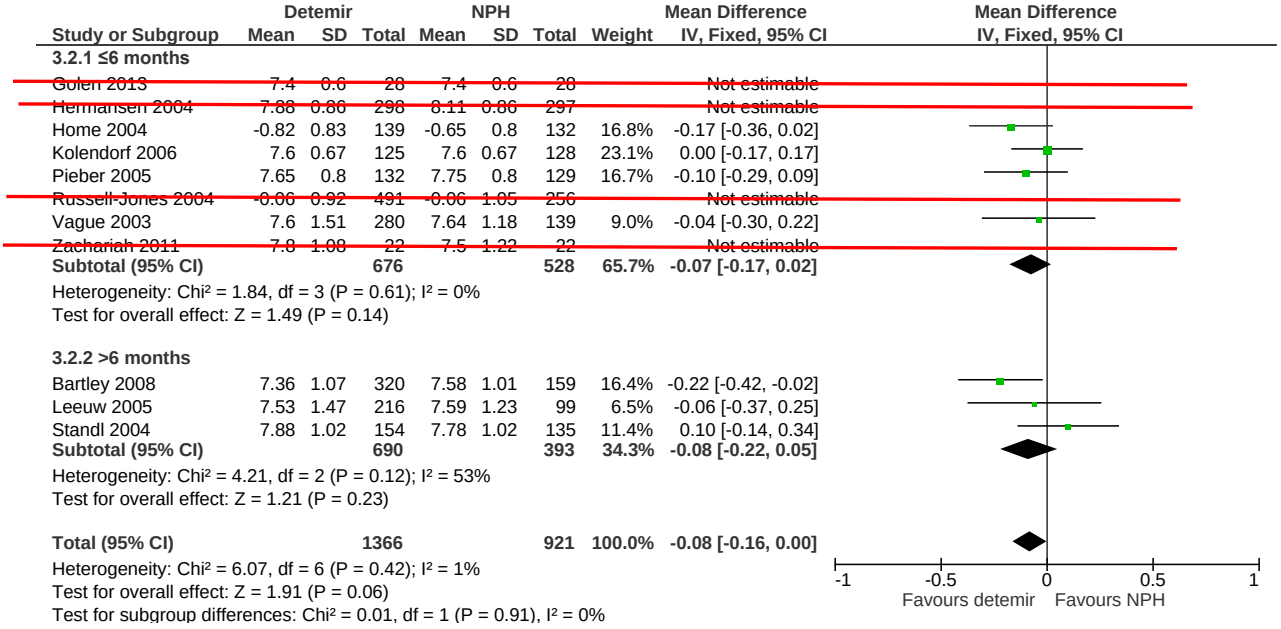


Figure 118: HbA1c – studies using current clinical practice regimen



J.4.2.3 Detemir versus NPH - heterogeneity

There was significant heterogeneity between trials for the outcome of HbA1c at less than or equal to 6 months and >6 months in the meta-analysis for Detemir vs. NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the significant heterogeneity disappeared. However the effect size and 95% CI hardly changed.

Figure 119: Body weight change

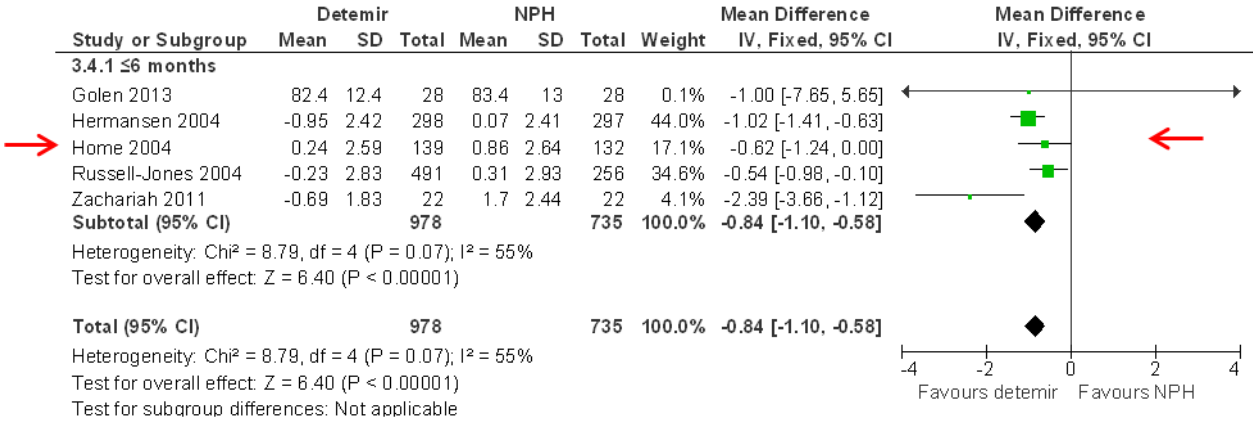


Figure 120: Major hypoglycaemia (no. of patients)

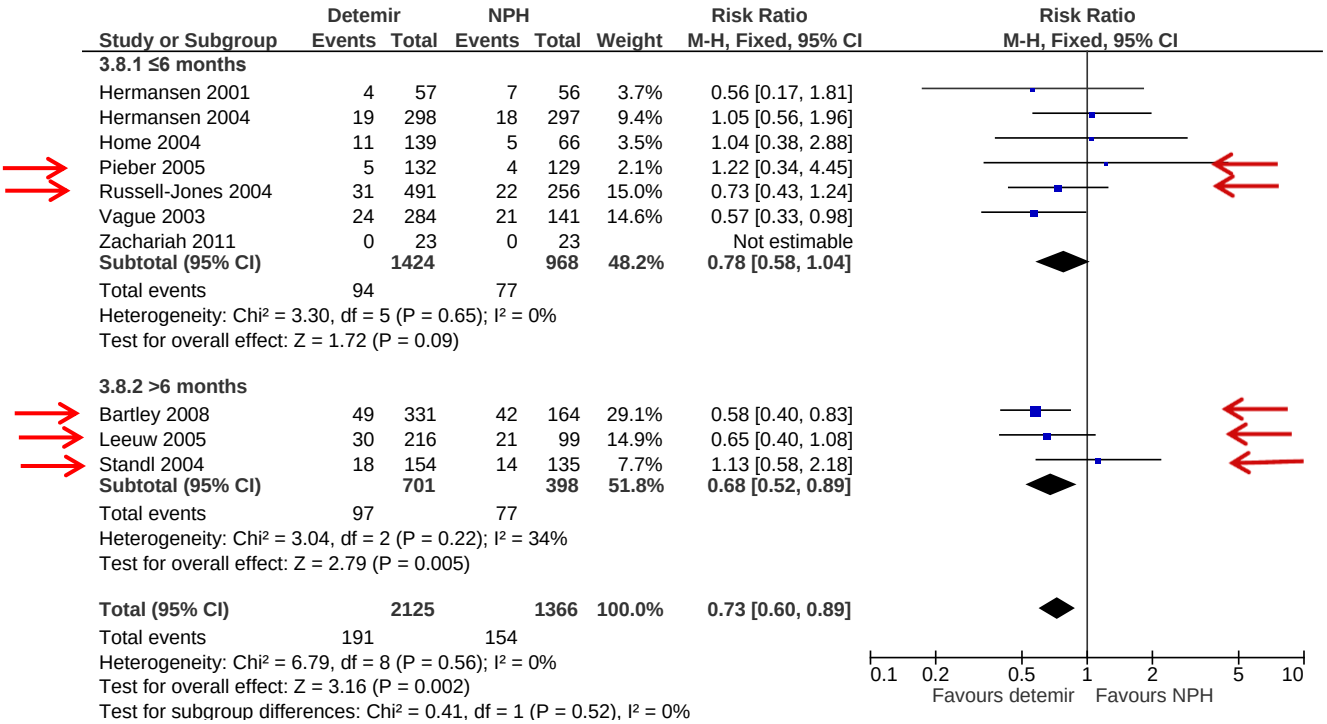
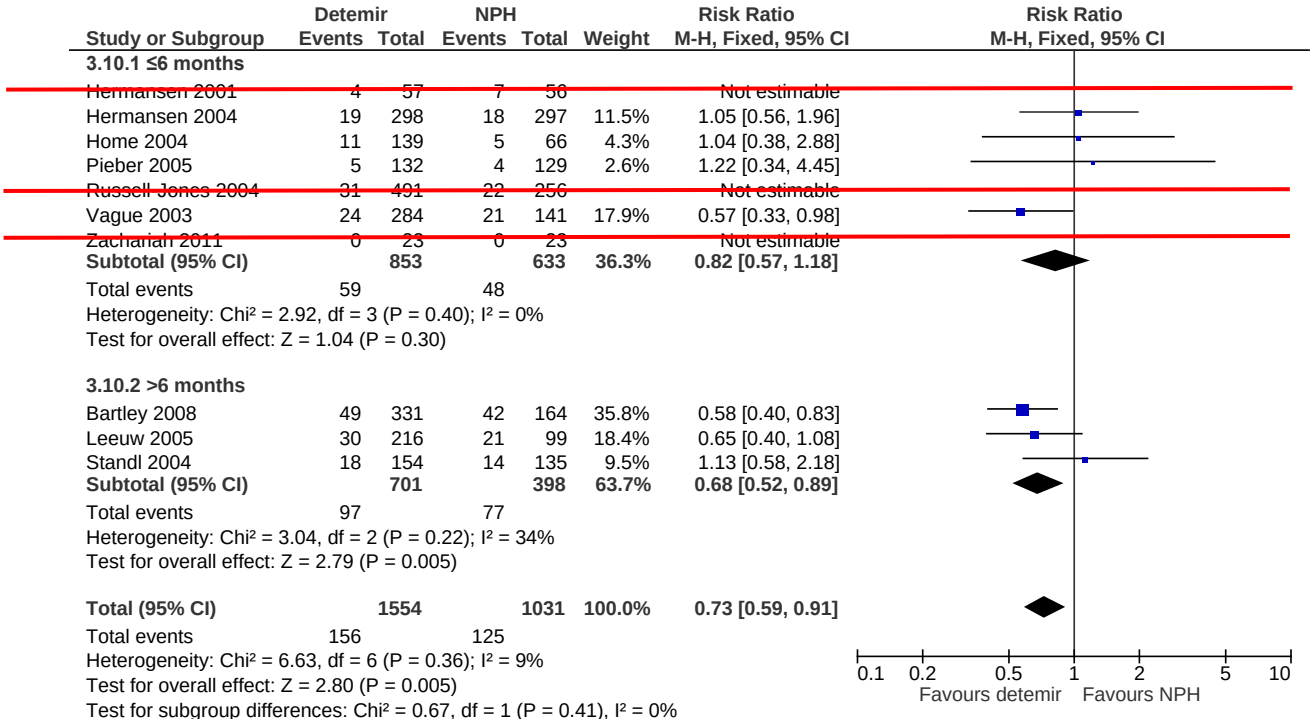


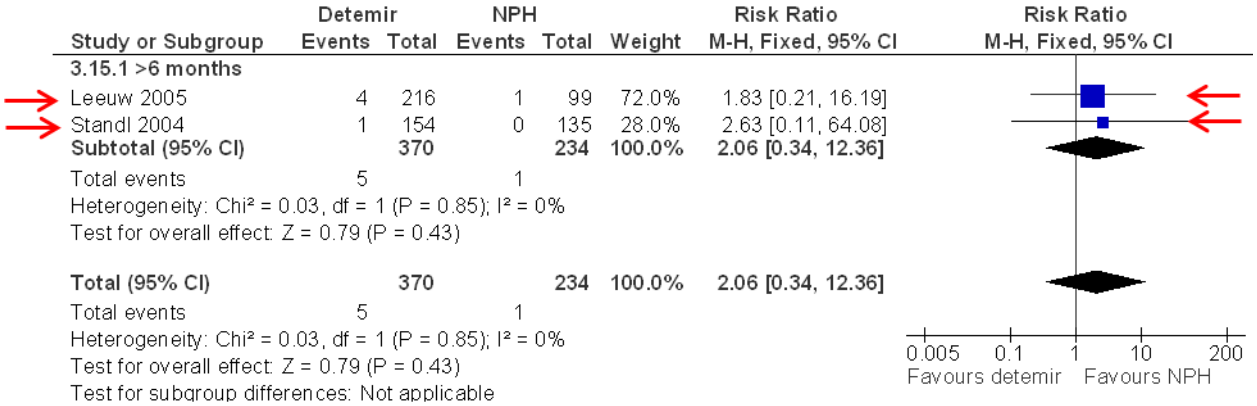
Figure 121: Major hypoglycaemia (no. of patients) – studies using current clinical practice regimen



J.4.2.4 Detemir versus NPH - heterogeneity

There was visible heterogeneity between trials for the outcome of major hypoglycaemia at less than and equal to 6 months and more than 6 months in the meta-analysis for detemir versus NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the data still looked heterogeneous. However, the effect size and 95% CI dramatically changed from a statistically significant benefit of Detemir at 6 months, to NS difference between the groups.

Figure 122: Injection site reactions



J.4.2.5 Detemir versus Glargine (less than or equal to 6 months and more than 6 months)

Figure 123: HbA1c % (change from baseline)

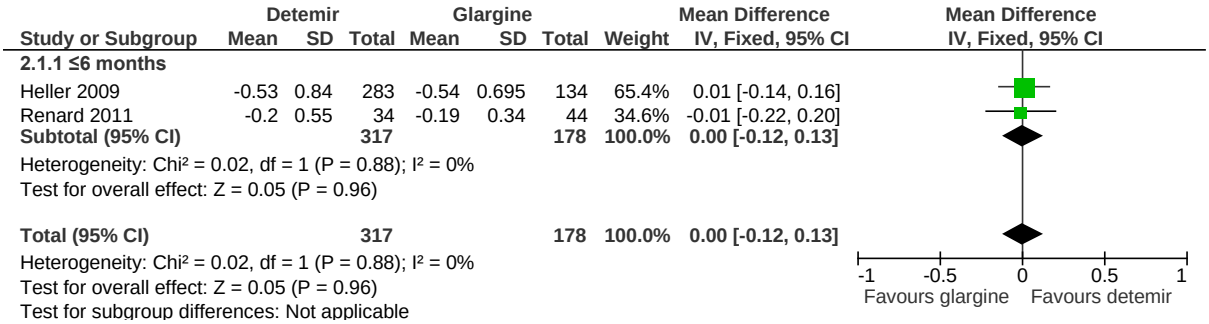


Figure 124: HbA1c less than or equal to 7% without hypoglycaemia

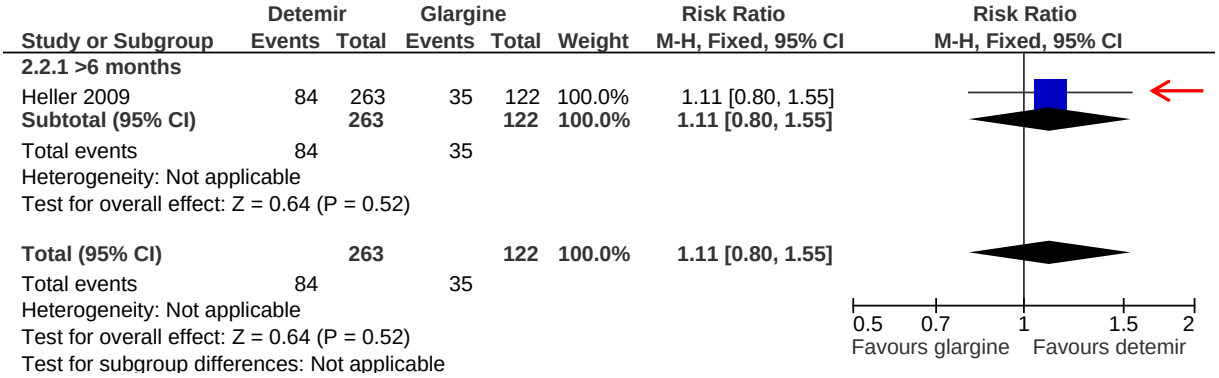


Figure 125: Severe symptomatic hypoglycaemia

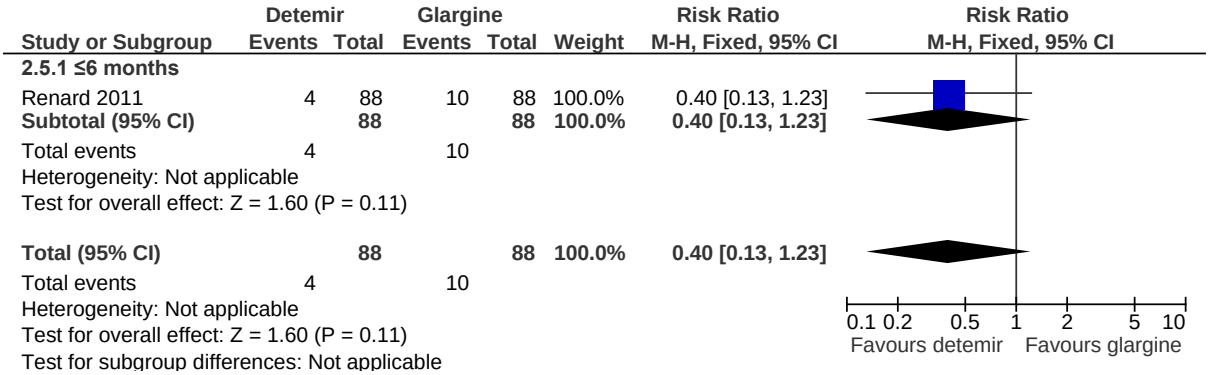
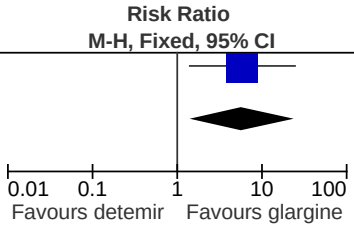


Figure 126: Injection site reactions

Study or Subgroup	Detemir Events	Detemir Total	Glargine Events	Glargine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Heller 2009	24	300	2	147	100.0%	5.88 [1.41, 24.54]
Total (95% CI)		**300**		**147**	**100.0%**	**5.88 [1.41, 24.54]**
Total events	24		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.43 (P = 0.02)



J.4.2.6 Glargine versus NPH (less than and equal to 6 months and more than 6 months)

Figure 127: HbA1c

Study or Subgroup	Glargine 30 Mean	Glargine 30 SD	Glargine 30 Total	NPH Mean	NPH SD	NPH Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 ≤6 months								
Bolli 2009	7.26	0.74	85	7.26	0.98	90	1.5%	0.00 [-0.26, 0.26]
Home 2005	-0.21	0.85	292	-0.1	0.86	293	5.0%	-0.11 [-0.25, 0.03]
Pieber 2000	-0.25	0.52	110	-0.03	0.52	109	5.0%	-0.22 [-0.36, -0.08]
Raskin 2000	7.5	1.19	264	7.6	1.14	270	2.4%	-0.10 [-0.30, 0.10]
Ratner 2000	-0.16	0.8	256	-0.21	0.81	262	5.0%	0.05 [-0.09, 0.19]
Rosenstock 2000	-0.4	0.48	82	-0.4	0.48	88	4.6%	0.00 [-0.14, 0.14]
Rossetti 2003	6.6	0.4	17	7	0.4	17	1.3%	-0.40 [-0.67, -0.13]
Subtotal (95% CI)			**1106**			**1129**	**24.8%**	**-0.09 [-0.15, -0.03]**
Heterogeneity: Chi² = 14.50, df = 6 (P = 0.02); I² = 59%								
Test for overall effect: Z = 2.78 (P = 0.005)								
4.1.2 >6 months								
Porcelatti 2004	6.7	0.1	61	7.1	0.1	60	75.2%	-0.40 [-0.44, -0.36]
Subtotal (95% CI)			**61**			**60**	**75.2%**	**-0.40 [-0.44, -0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 22.00 (P < 0.00001)								
Total (95% CI)			**1167**			**1189**	**100.0%**	**-0.32 [-0.35, -0.29]**
Heterogeneity: Chi² = 87.48, df = 7 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 20.46 (P < 0.00001)								
Test for subgroup differences: Chi² = 72.98, df = 1 (P < 0.00001), I² = 98.6%								

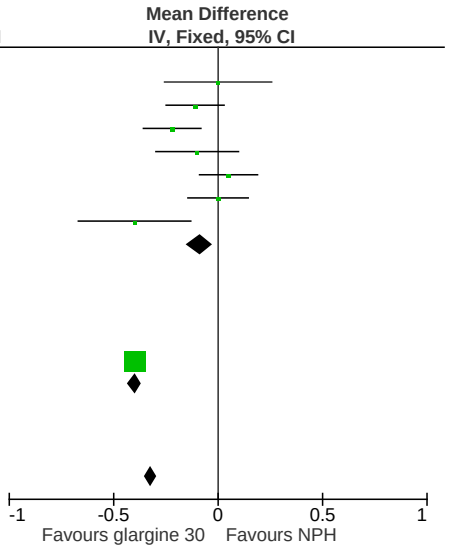


Figure 128: Severe hypoglycaemia

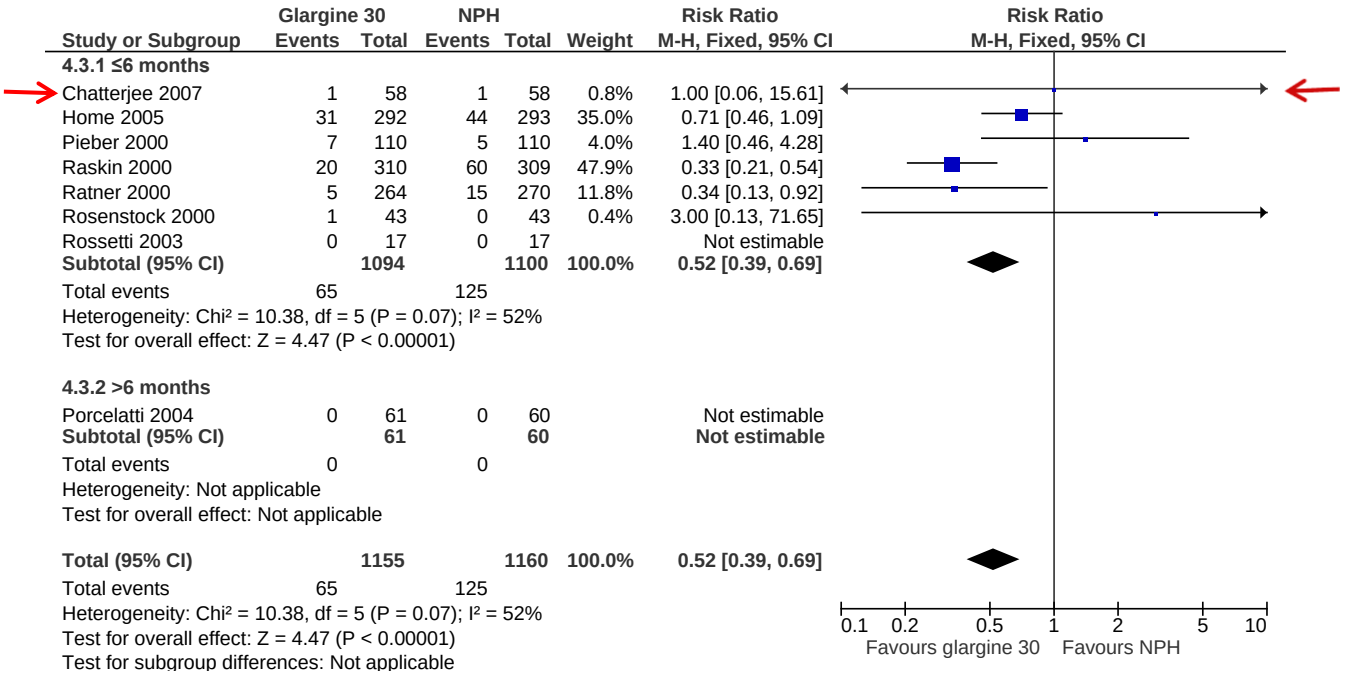
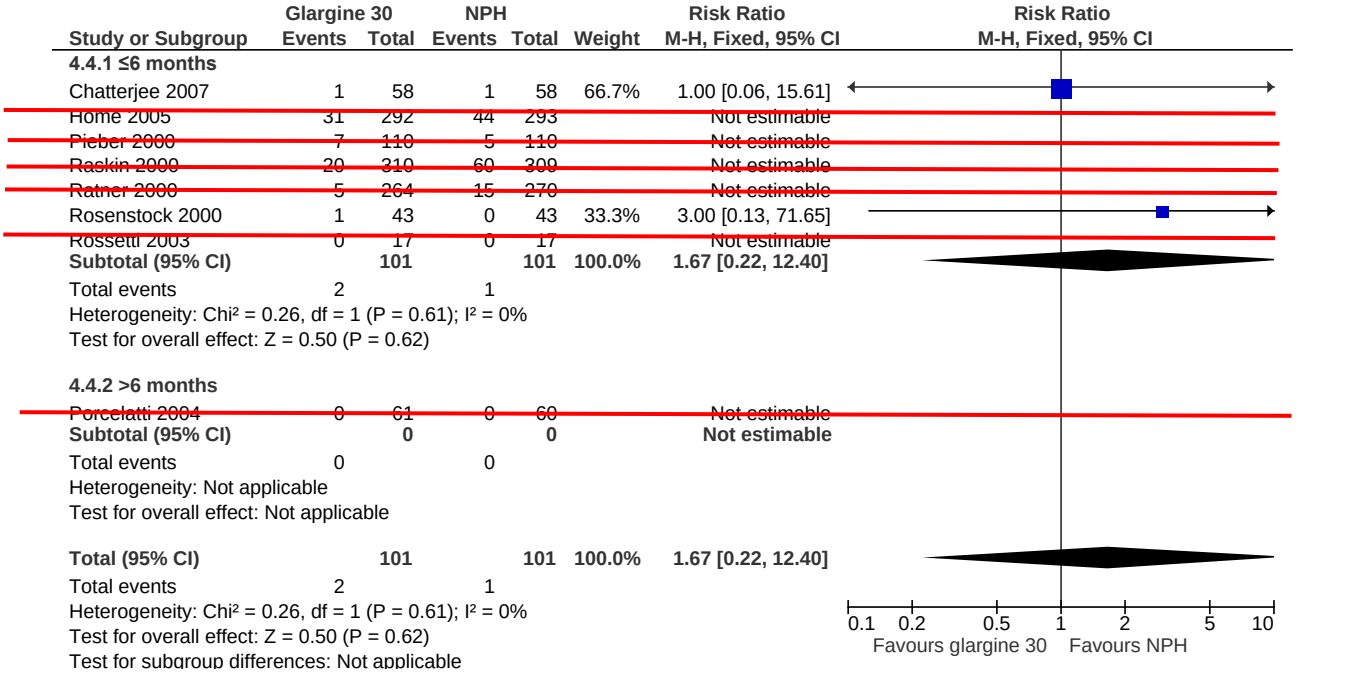


Figure 129: Severe hypoglycaemia – studies using current clinical practice regimen



J.4.2.7 Glargine versus NPH - heterogeneity

There was significant heterogeneity between trials for the outcome of severe hypoglycaemia at less than or equal to 6 months in the meta-analysis for Glargine vs. NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the significant heterogeneity

disappeared and there were only 2 studies left. However, the effect size and 95% CI drastically changed from a statistically significant benefit of glargine, to NS difference between the groups at less than or equal to 6 months.

Figure 130: Glargine versus NPH - heterogeneity

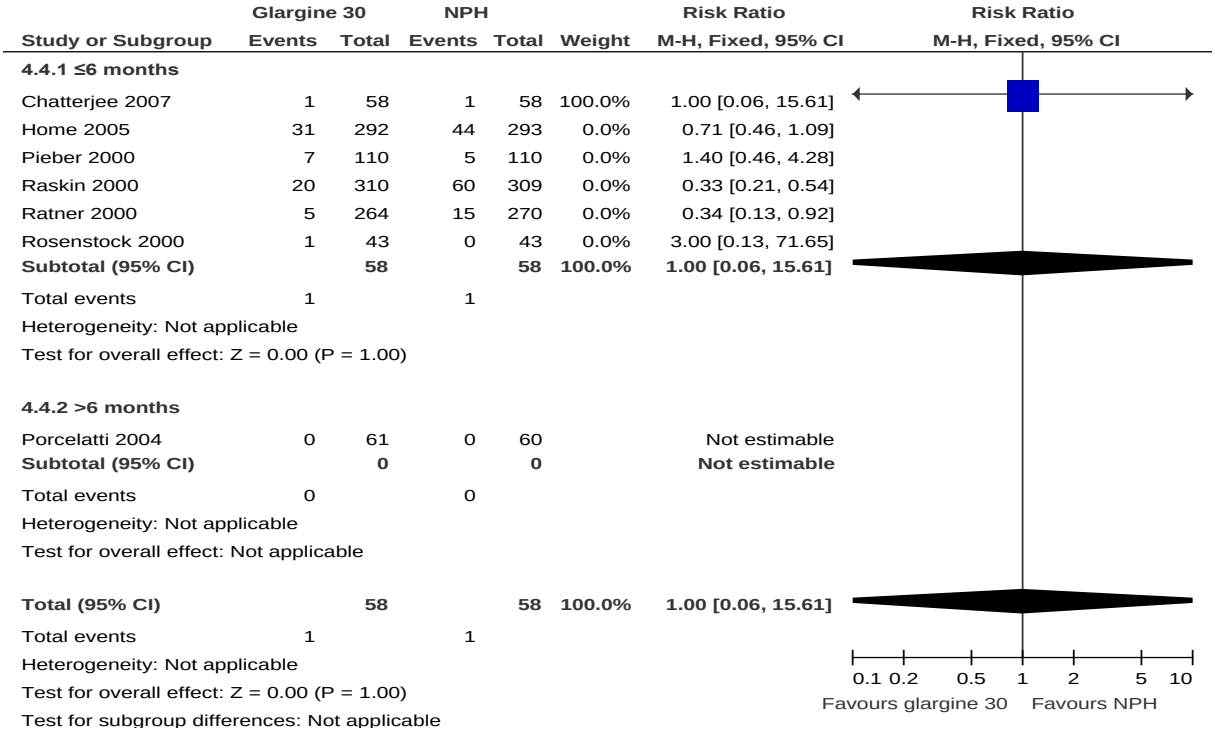


Figure 131: Injection site reactions

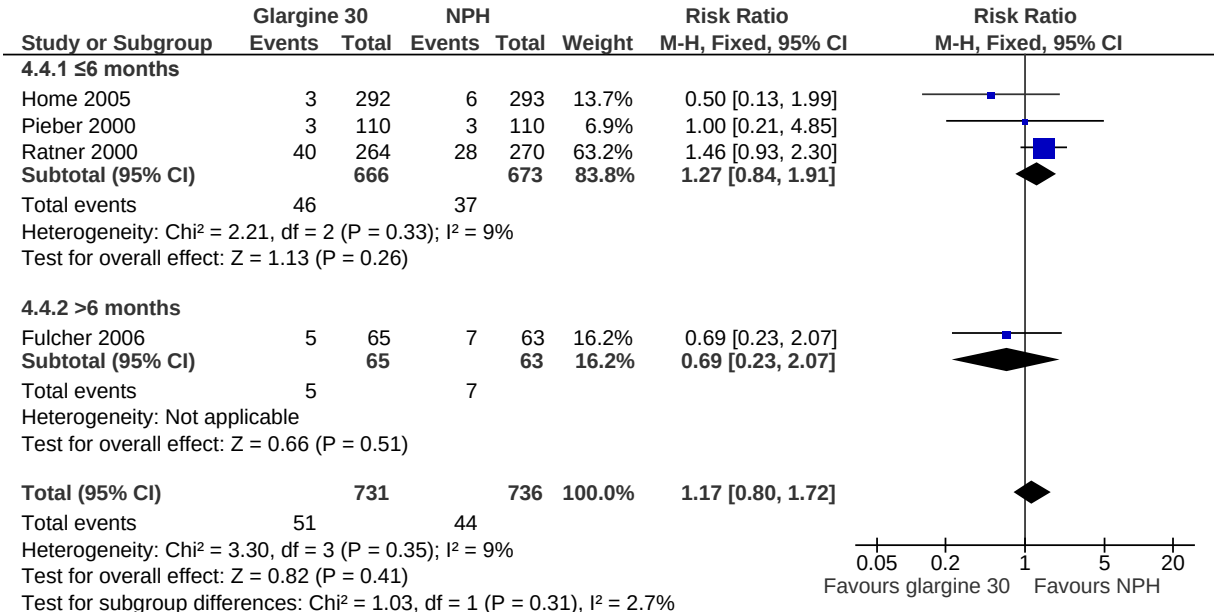
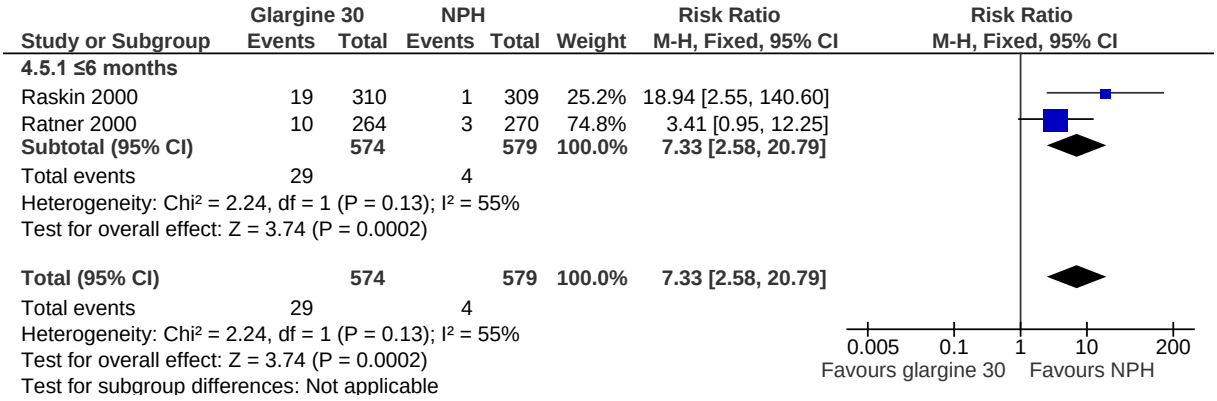


Figure 132: Injection site pain



J.4.2.9 Degludec versus Detemir (less than or equal to 6 months and more than 6 months)

Figure 133: Severe hypoglycaemia – no. of patients

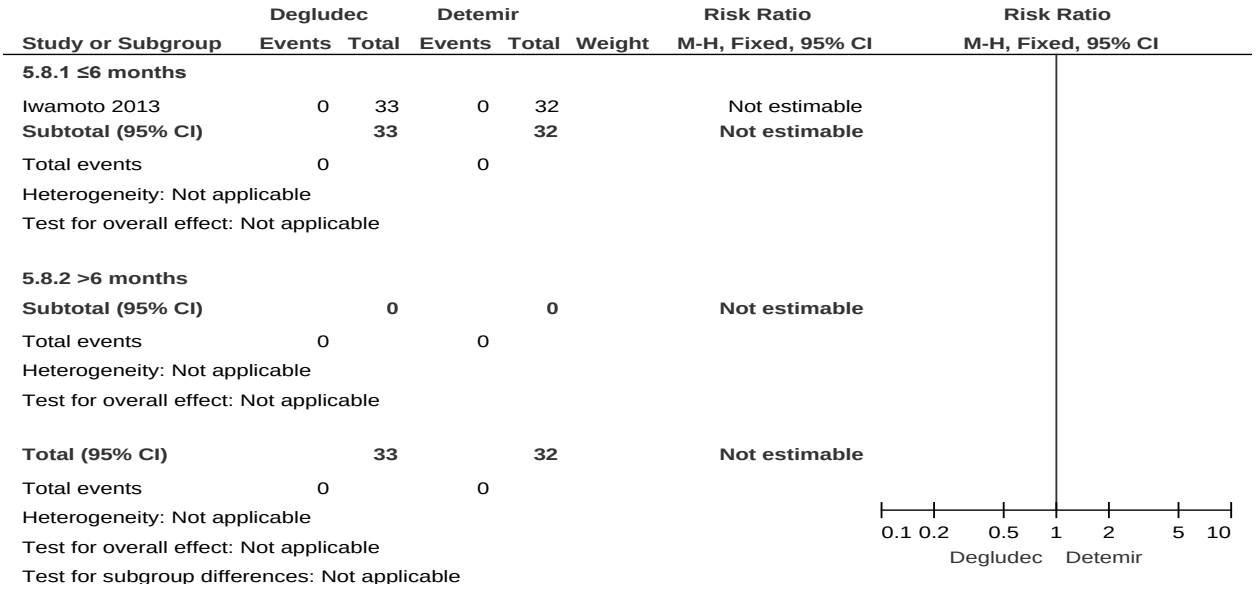


Figure 134: Severe hypoglycaemia – regimen current clinical practice

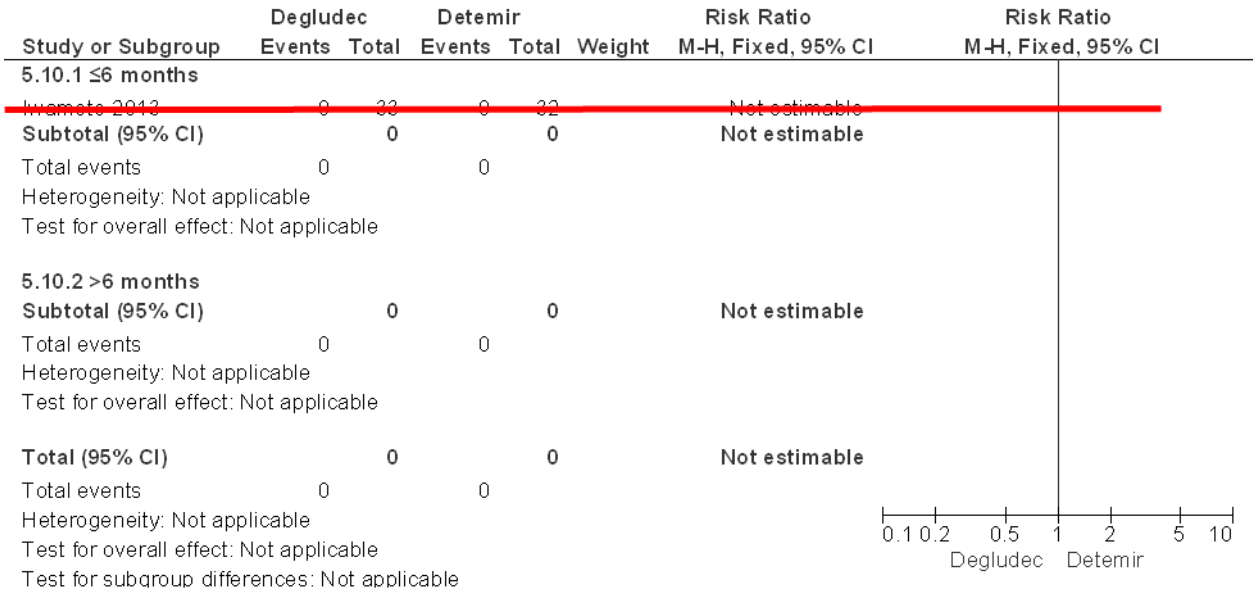


Figure 135: Adverse events

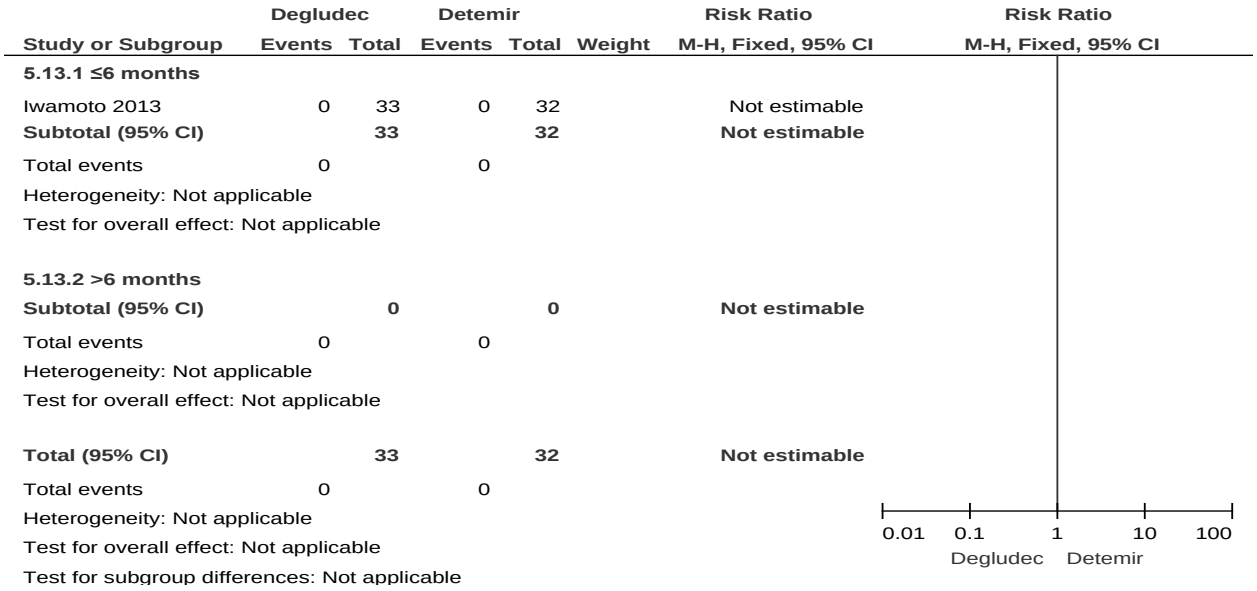
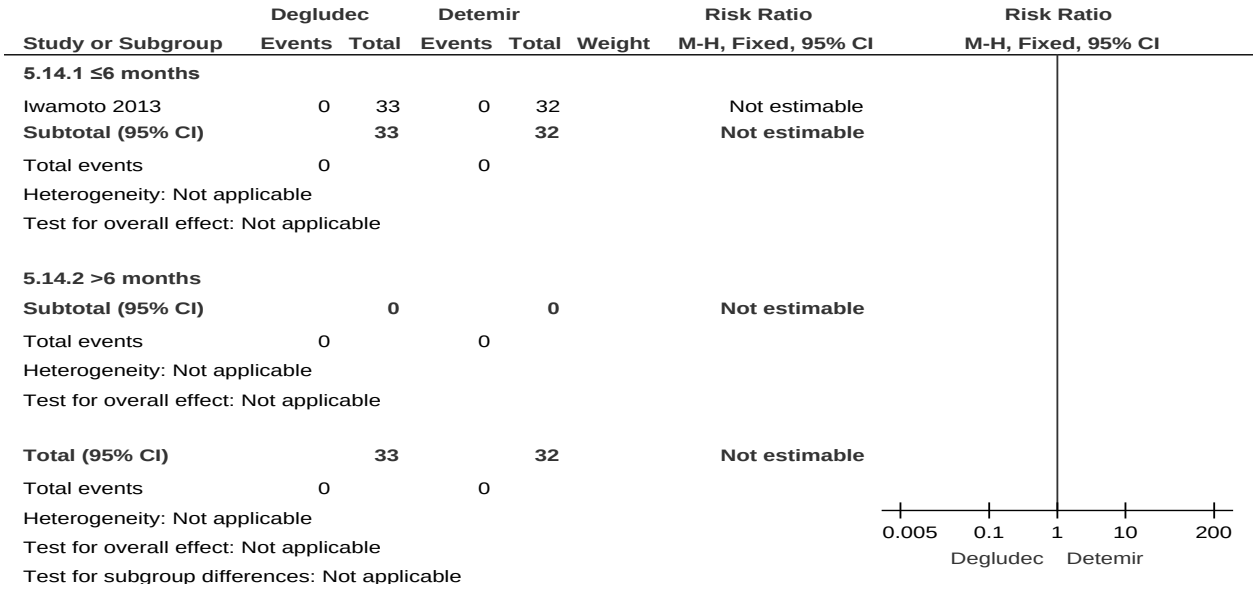


Figure 136: Serious adverse events



J.4.3 Mixed insulin

J.4.3.1 INSULIN: Mix versus basal-bolus (less than or equal to 6 months)

Human mix

Figure 137: HbA1c – final value (less than or equal to 6 months)

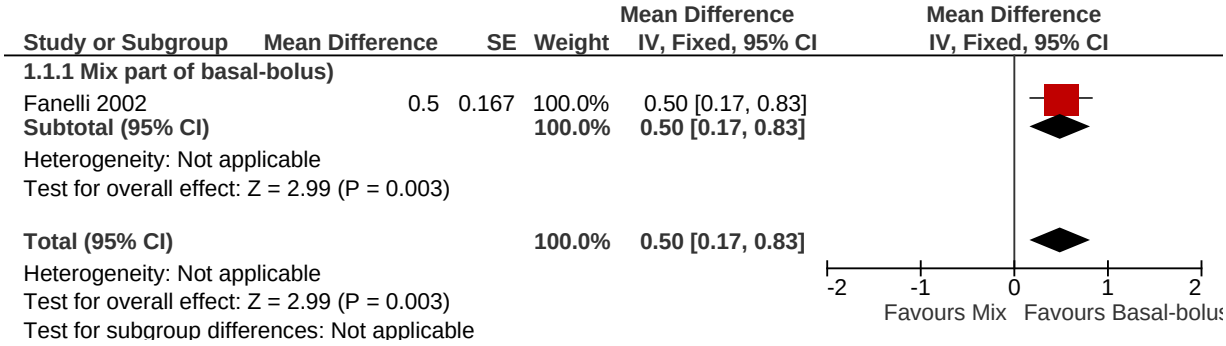


Figure 138: Nocturnal hypoglycaemia - episodes/patient-day (less than or equal to 6 months)

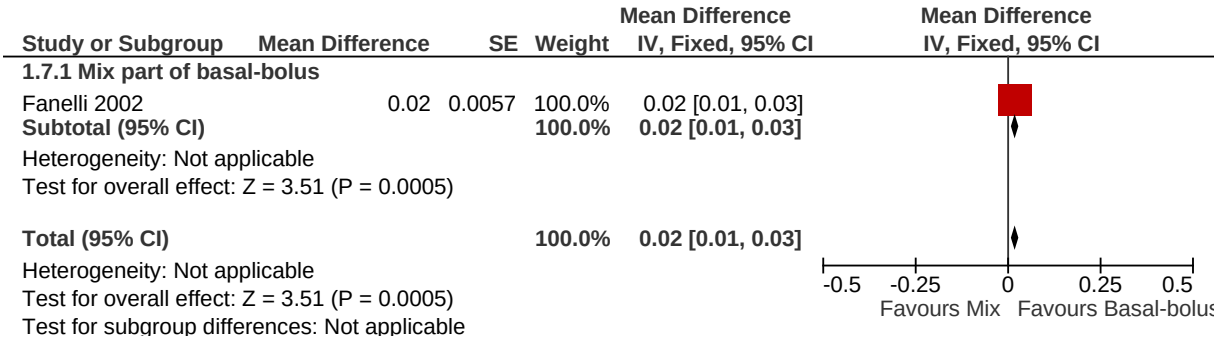


Figure 139: Severe/major hypoglycaemia – no. of patients (less than or equal to 6 months)

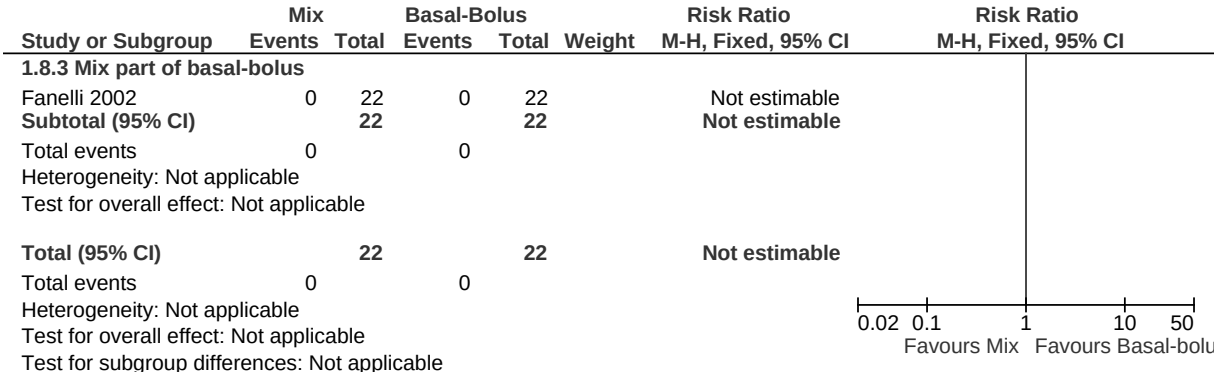


Figure 140: Ketoacidosis – no. of patients (less than or equal to 6 months)

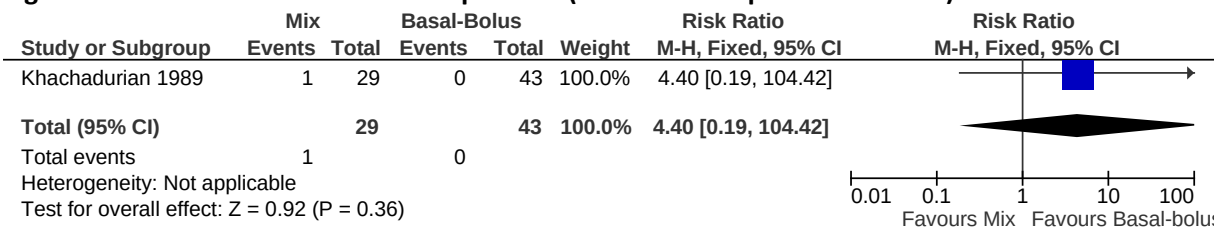
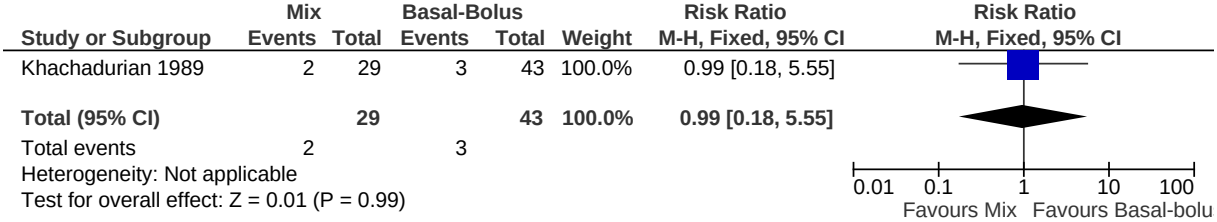


Figure 141: Injection site reactions – no. of pts (less than or equal to 6 months)



Lispro Mix

Figure 142: HbA1c – final value (less than or equal to 6 months)

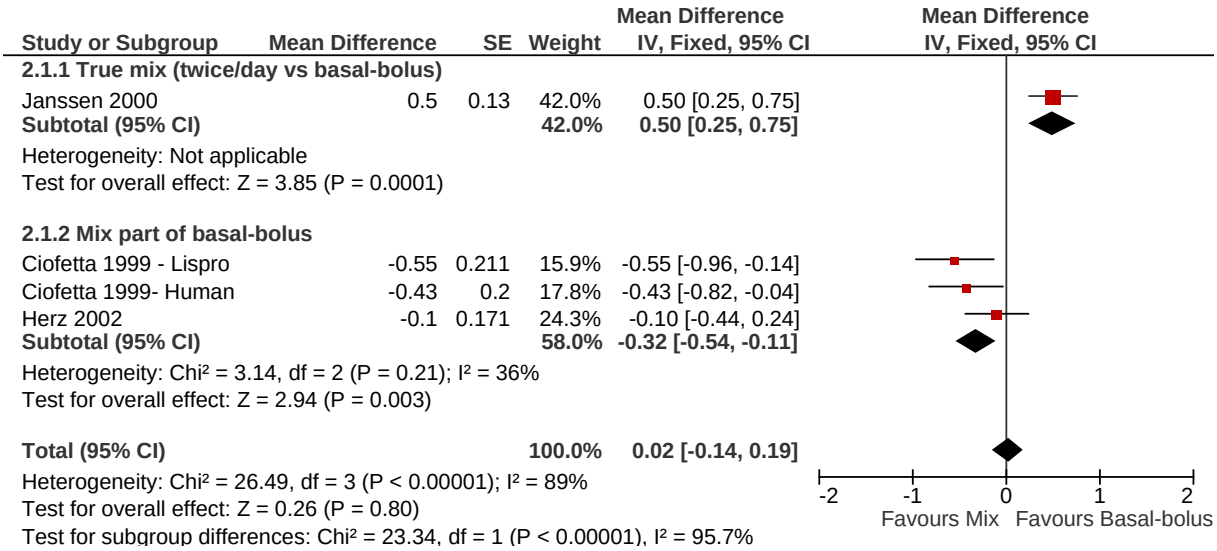


Figure 143: Hypoglycaemia – episodes/pt (less than or equal to 6 months)

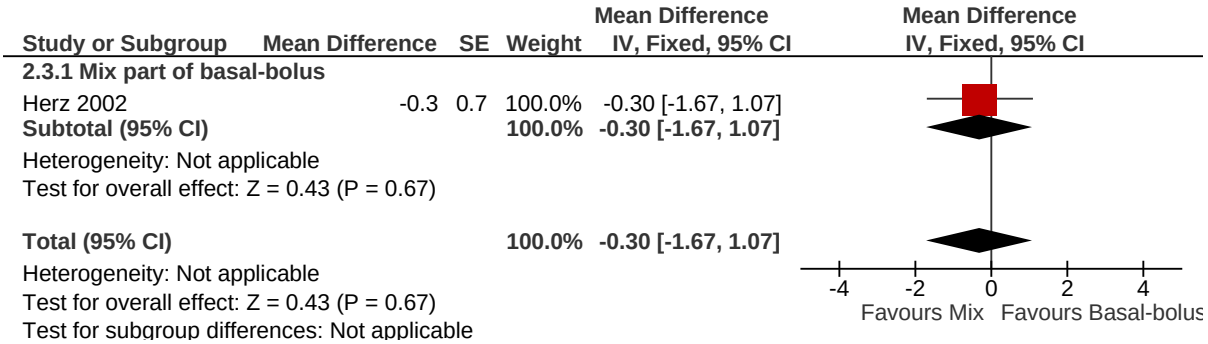


Figure 144: Hypoglycaemia – episodes/patient/month (less than or equal to 6 months)

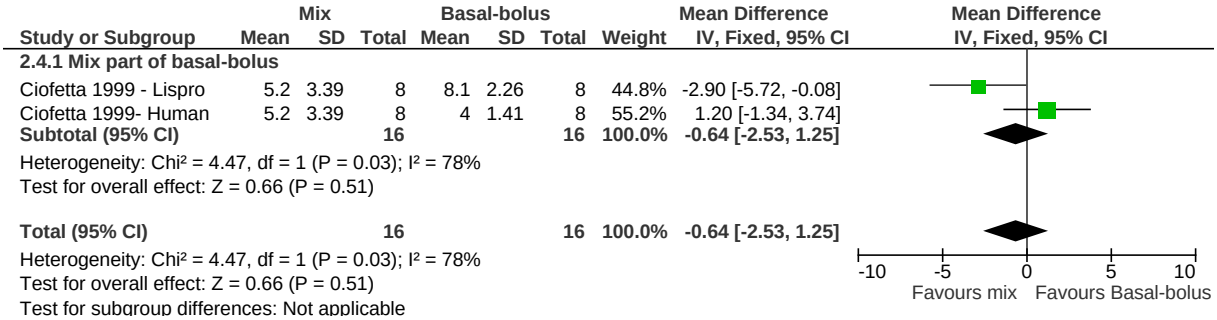


Figure 145: Nocturnal hypoglycaemia – no. of patients (less than or equal to 6 months)

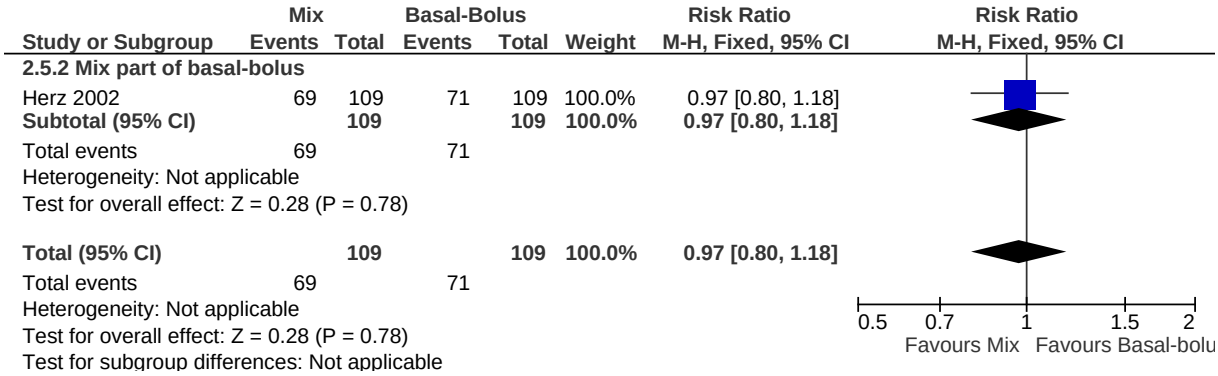


Figure 146: Severe/major hypoglycaemia – no. of patients (less than or equal to 6 months)

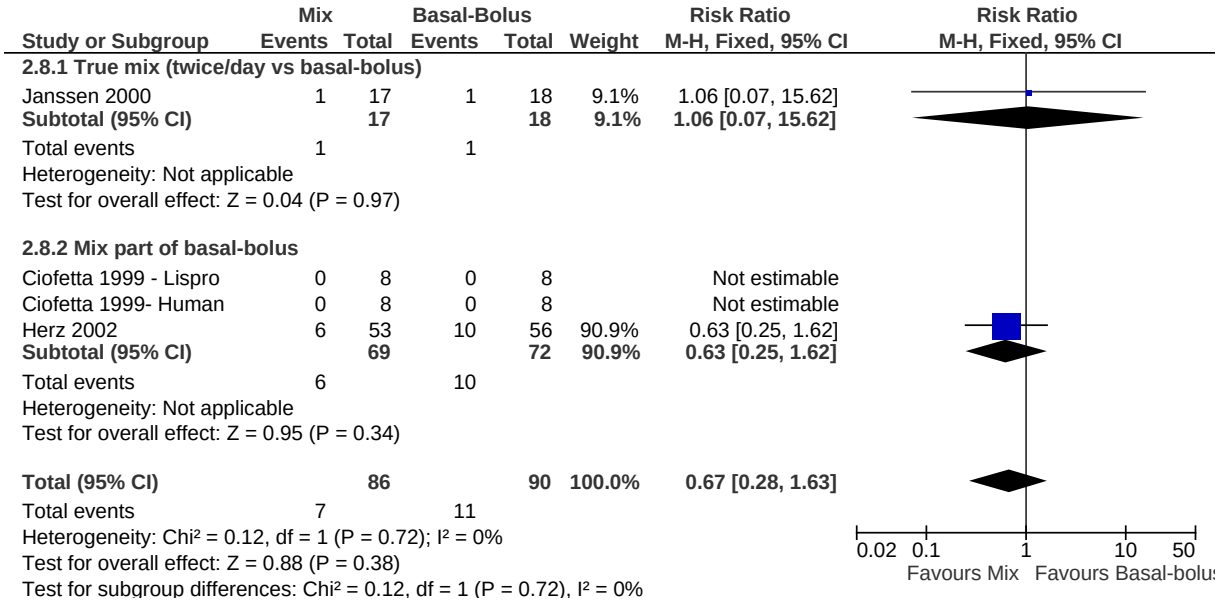
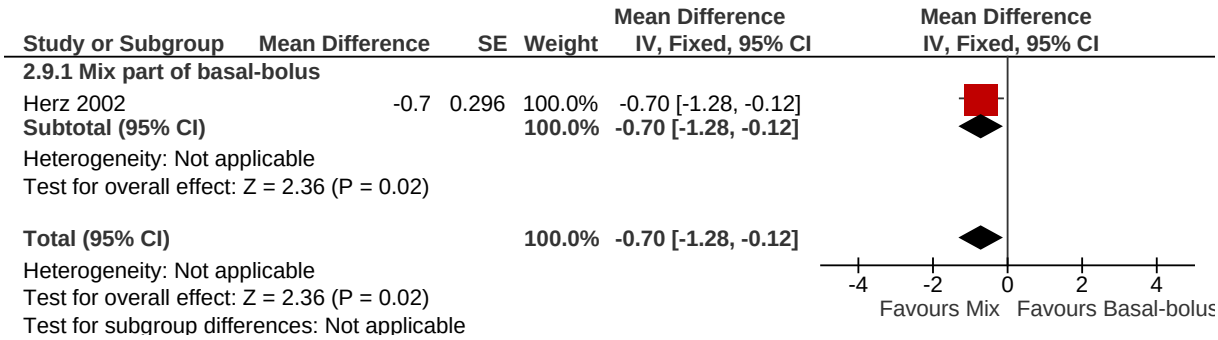


Figure 147: Weight change - kg (less than or equal to 6 months)



Aspart mix

Figure 148: Hypoglycaemia – no. of patients (less than or equal to 6 months)

Study or Subgroup	Mix Events	Mix Total	Basal-Bolus Events	Basal-Bolus Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Mix part of basal-bolus						
Hirsch 2012B	341	362	168	180	100.0%	1.01 [0.96, 1.06]
Subtotal (95% CI)		**362**		**180**	**100.0%**	**1.01 [0.96, 1.06]**
Total events	341		168			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**362**		**180**	**100.0%**	**1.01 [0.96, 1.06]**
Total events	341		168			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

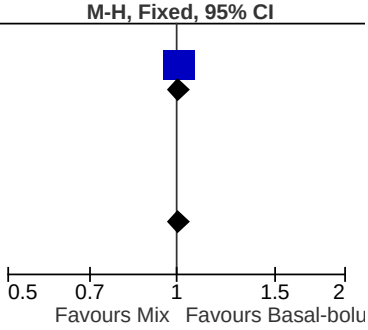


Figure 149: Nocturnal hypoglycaemia – no. of patients (less than or equal to 6 months)

Study or Subgroup	Mix Events	Mix Total	Basal-Bolus Events	Basal-Bolus Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Mix part of basal-bolus						
Hirsch 2012B	192	362	125	180	100.0%	0.76 [0.67, 0.88]
Subtotal (95% CI)		**362**		**180**	**100.0%**	**0.76 [0.67, 0.88]**
Total events	192		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.85 (P = 0.0001)						
Total (95% CI)		**362**		**180**	**100.0%**	**0.76 [0.67, 0.88]**
Total events	192		125			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.85 (P = 0.0001)						
Test for subgroup differences: Not applicable						

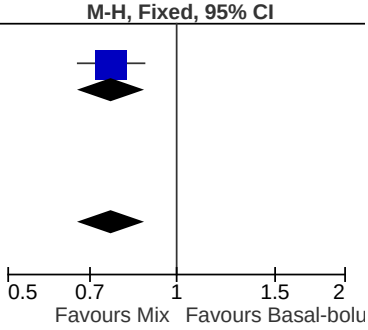


Figure 150: Severe/major hypoglycaemia – no. of patients (less than or equal to 6 months)

Study or Subgroup	Mix Events	Mix Total	Basal-Bolus Events	Basal-Bolus Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 Mix part of basal-bolus						
Chen 2006	2	27	1	27	3.3%	2.00 [0.19, 20.77]
Hirsch 2012B	35	362	22	180	96.7%	0.79 [0.48, 1.31]
Subtotal (95% CI)		**389**		**207**	**100.0%**	**0.83 [0.51, 1.35]**
Total events	37		23			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**389**		**207**	**100.0%**	**0.83 [0.51, 1.35]**
Total events	37		23			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Test for subgroup differences: Not applicable						

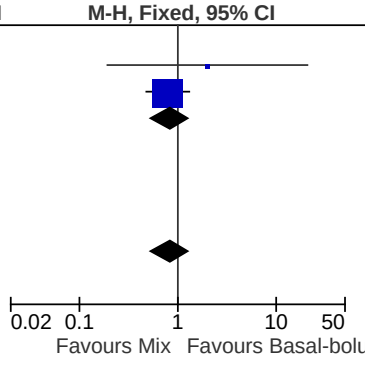


Figure 151: SF-36 Physical (less than or equal to 6 months)

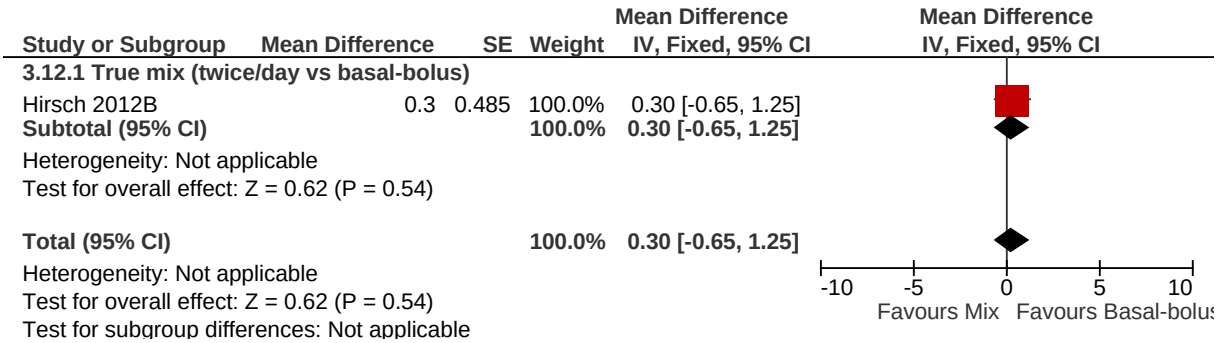


Figure 152: SF-36 Mental (less than or equal to 6 months)

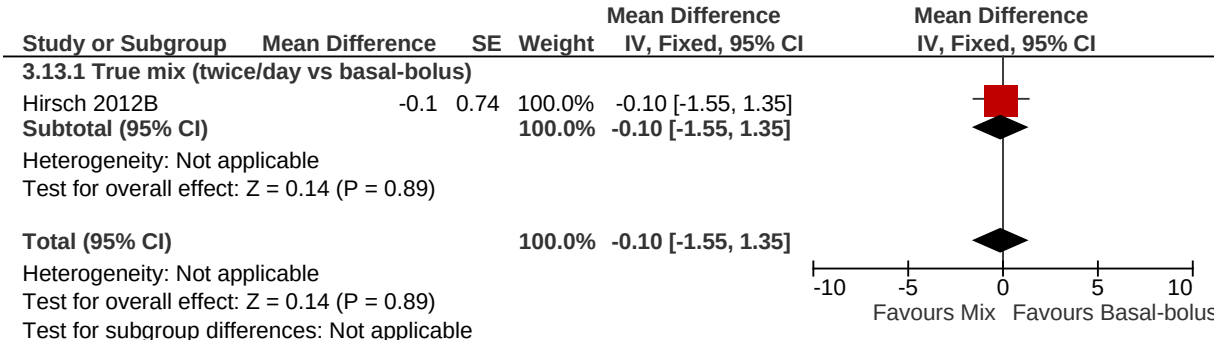


Figure 153: Treatment satisfaction - % (less than or equal to 6 months) – Lispro or Aspart

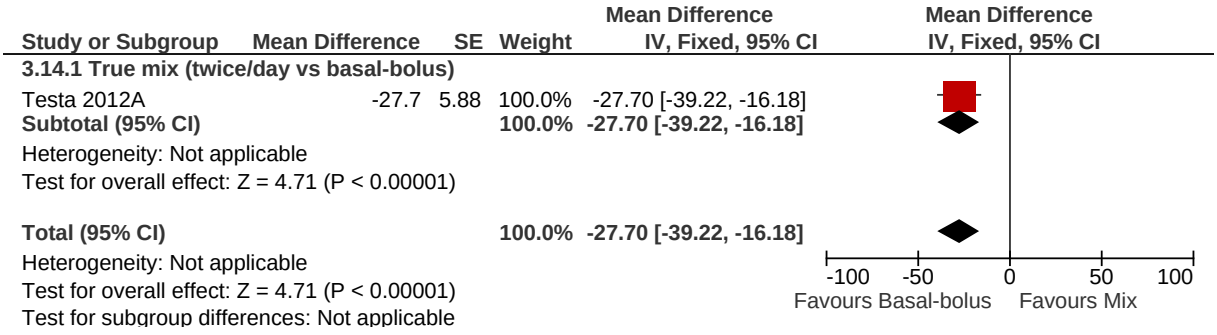
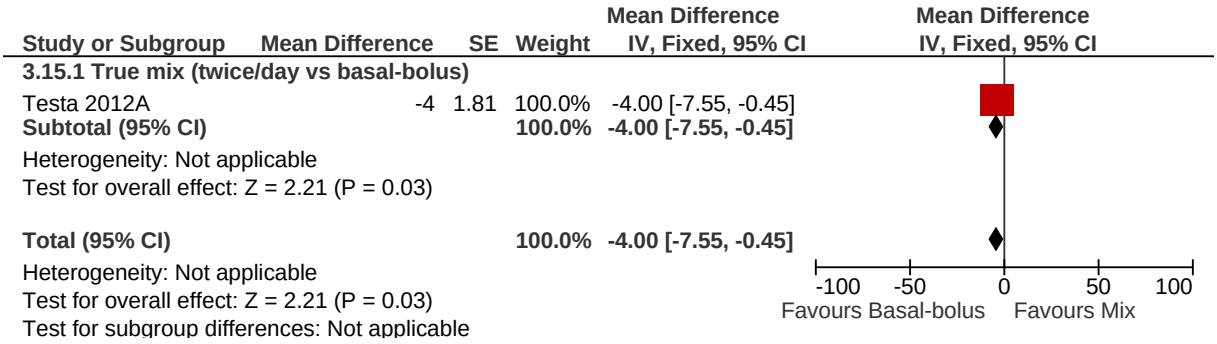


Figure 154: Regimen acceptance - % (less than or equal to 6 months) – Lispro or Aspart



J.4.3.2 INSULIN: Mix versus mix (less than or equal to 6 months)

Figure 155: HbA1c – final value

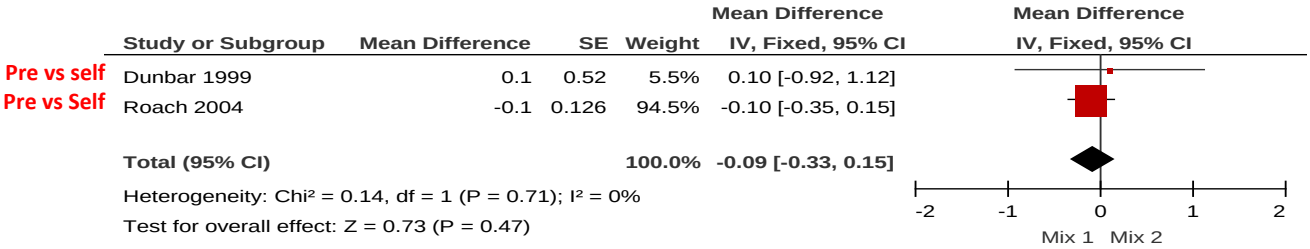


Figure 156: Severe/major hypoglycaemia – no. of patients

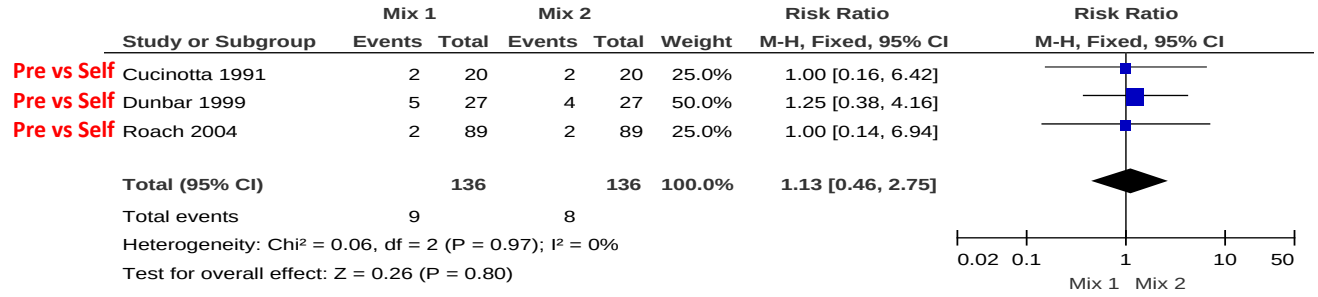
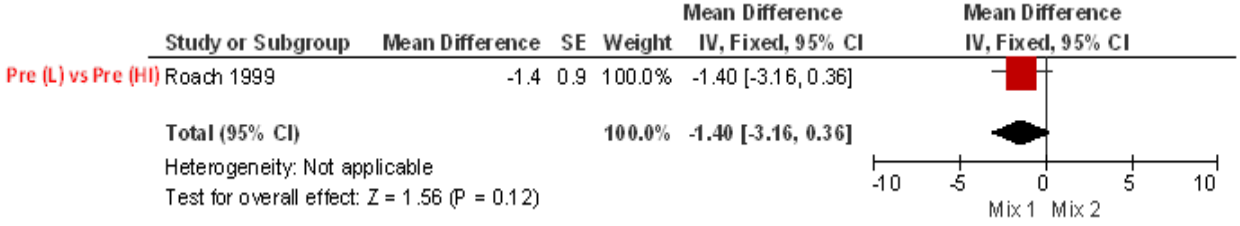


Figure 157: Nocturnal hypoglycaemia – episodes/patient



J.4.4 Adjuncts

J.4.4.1 Pramlintide

Figure 158: HbA1c % less than or equal to 6 months follow-up

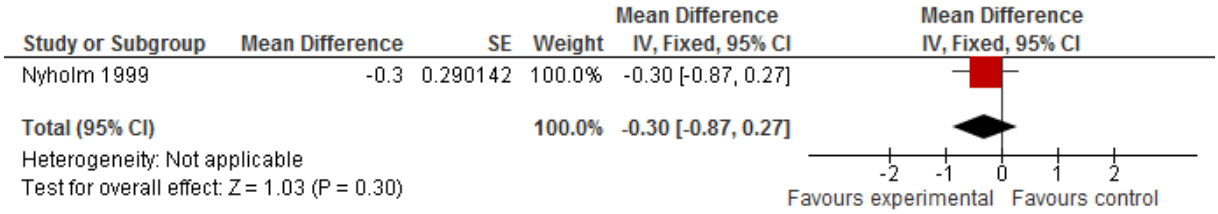


Figure 159: HbA1c (%) > 6 months follow-up

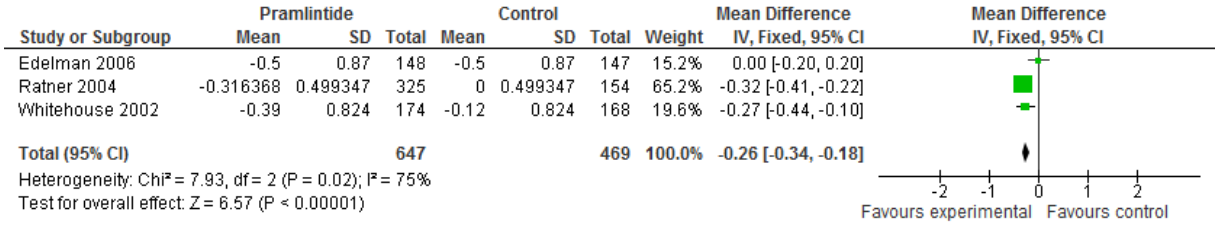


Figure 160: Severe Hypoglycaemia less than or equal to 6 months follow-up

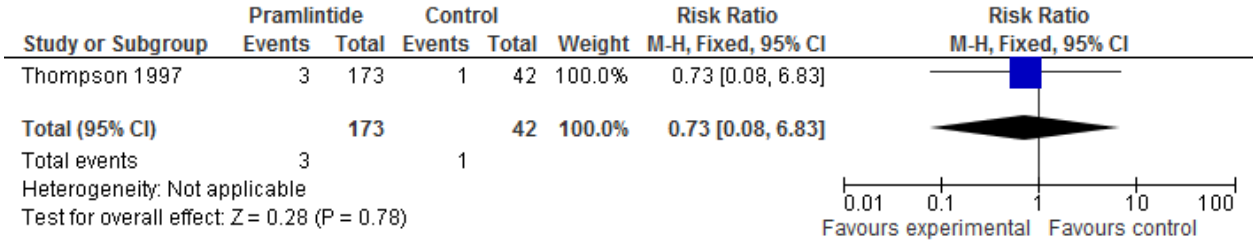


Figure 161: Symptoms of hypoglycaemia less than or equal to 6 months follow-up

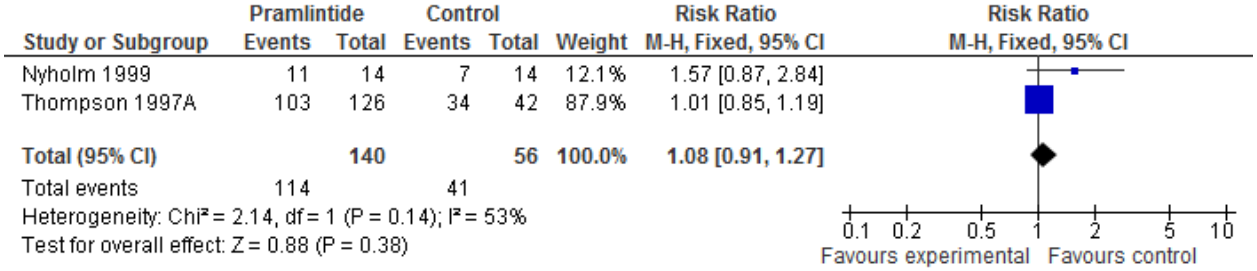


Figure 162: Symptoms of hypoglycaemia more than 6 months follow-up

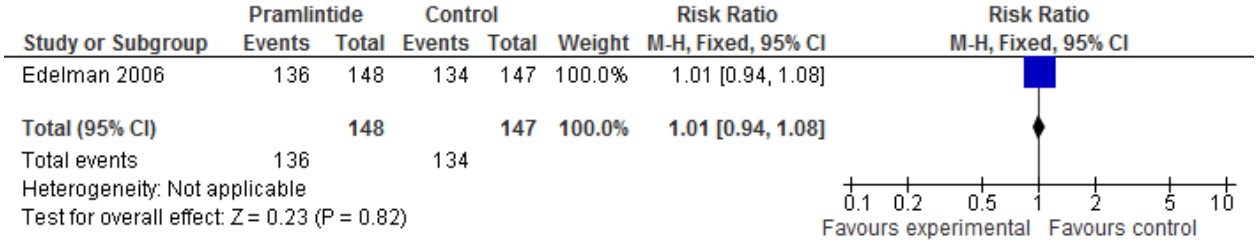


Figure 163: Adverse events - Gastrointestinal side effects less than or equal to 6 months follow-up

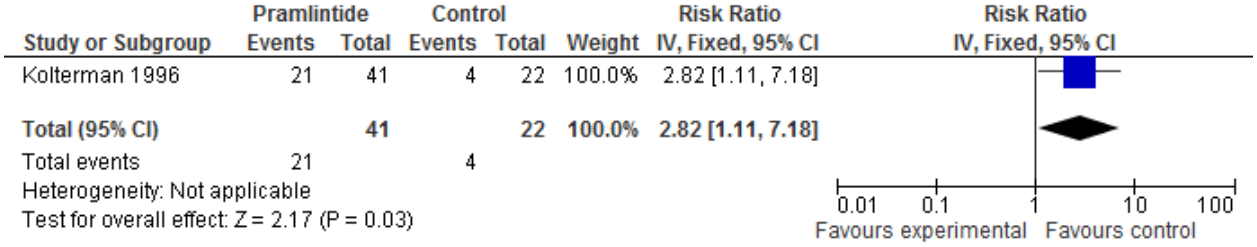


Figure 164: Adverse events – Nausea less than or equal to 6 months follow-up

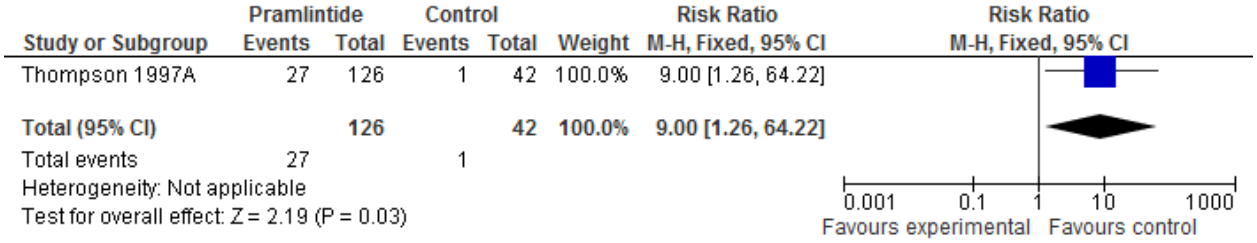


Figure 165: Adverse events – Nausea more 6 months follow-up

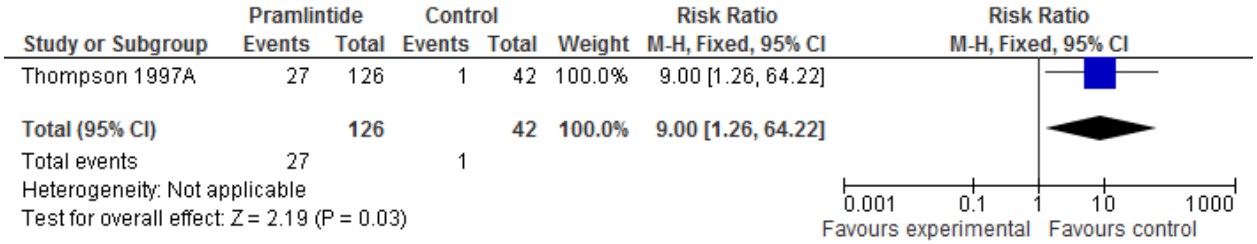


Figure 166: Vomiting less than or equal to 6 months follow-up

Study or Subgroup	Pramlintide Events	Pramlintide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelman 2006	20	148	9	147	100.0%	2.21 [1.04, 4.69]
Total (95% CI)		**148**		**147**	**100.0%**	**2.21 [1.04, 4.69]**
Total events	20		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)

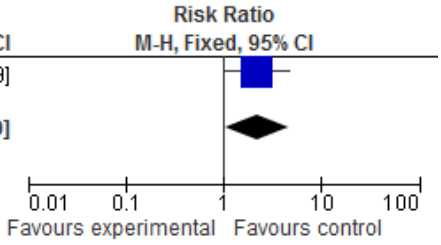


Figure 167: Anorexia less than or equal to 6 months follow-up

Study or Subgroup	Pramlintide Events	Pramlintide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Thompson 1997A	5	126	0	42	100.0%	3.72 [0.21, 65.97]
Total (95% CI)		**126**		**42**	**100.0%**	**3.72 [0.21, 65.97]**
Total events	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)

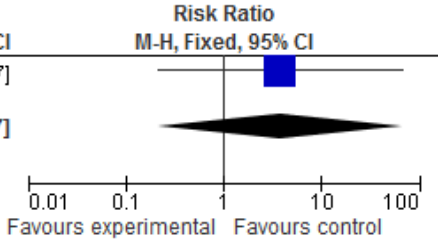


Figure 168: Anorexia more than 6 months follow-up

Study or Subgroup	Pramlintide Events	Pramlintide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelman 2006	13	142	3	147	100.0%	4.49 [1.31, 15.41]
Total (95% CI)		**142**		**147**	**100.0%**	**4.49 [1.31, 15.41]**
Total events	13		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)

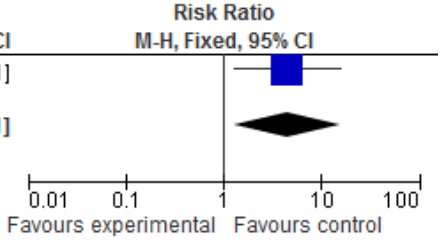


Figure 169: Dose of insulin less than or equal to 6 months follow-up

Study or Subgroup	Pramlintide Mean	Pramlintide SD	Pramlintide Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Edelman 2006	-12	0	148	1	0	147		Not estimable
Total (95% CI)			**148**			**147**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable

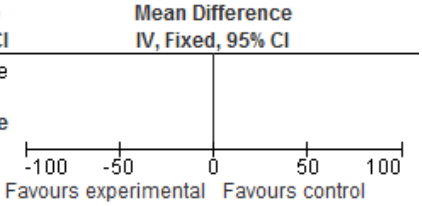


Figure 170: Weight change less than or equal to 6 months follow-up

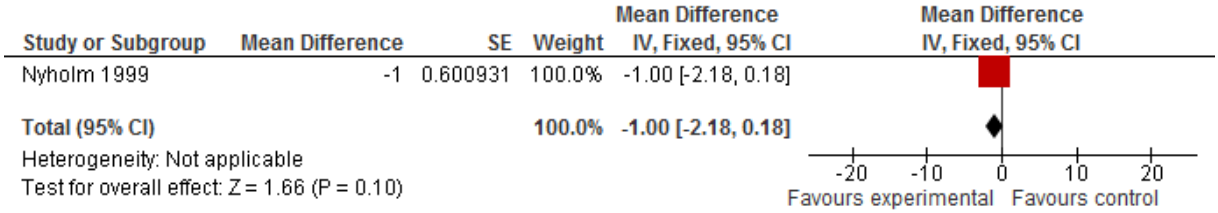
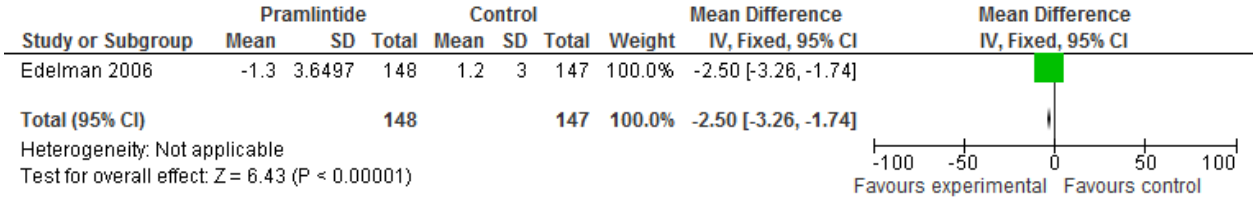


Figure 171: Weight change more than 6 months follow-up



J.4.4.2 Liraglutide

Figure 172: HbA1c % less than or equal to 6 months follow-up

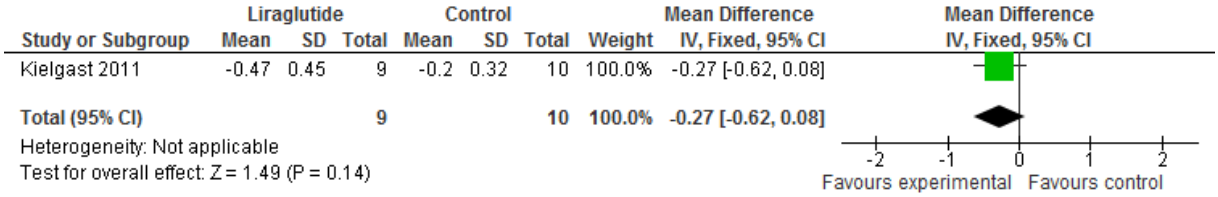


Figure 173: Dose of insulin less than or equal to 6 months follow-up

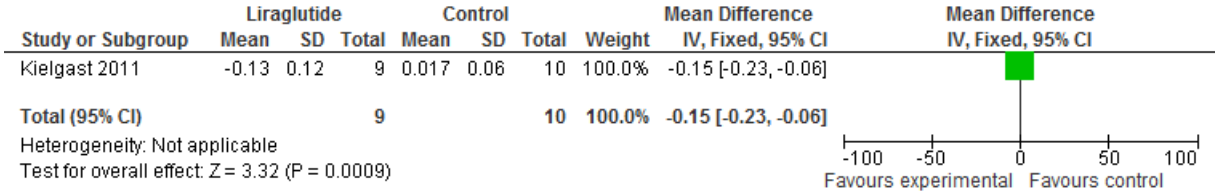
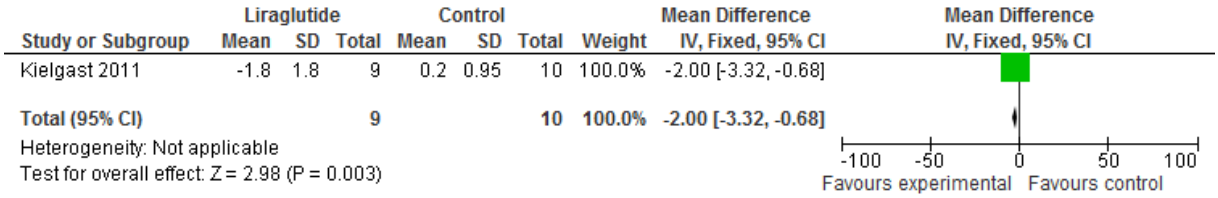


Figure 174: Weight change less than or equal to 6 months follow-up



J.4.4.3 Metformin

Figure 175: HbA1c % less than or equal to 6 months follow-up

Study or Subgroup	Metformin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Burchardt 2013	7.7	1.2	21	8.1	1.4	21	11.7%	-0.40 [-1.19, 0.39]
Jacobson 2009	-0.48	0.9	12	-0.17	0.6	11	18.9%	-0.31 [-0.93, 0.31]
Khan 2006	7.8	1.1	15	8.5	1.4	15	8.9%	-0.70 [-1.60, 0.20]
Meyer 2002	7.45	0.78	31	7.46	0.6	31	60.5%	-0.01 [-0.36, 0.34]
Total (95% CI)			**79**			**78**	**100.0%**	**-0.17 [-0.44, 0.10]**

Heterogeneity: Chi² = 2.67, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

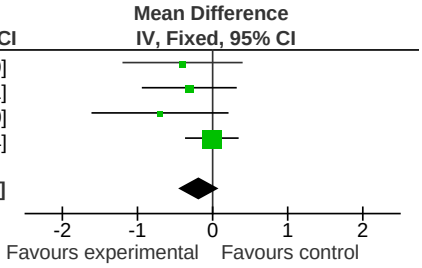


Figure 176: HbA1c % > 6 months follow-up

Study or Subgroup	Metformin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lund 2008	-0.1	0.78	48	-0.23	0.79	50	100.0%	0.13 [-0.18, 0.44]
Total (95% CI)			**48**			**50**	**100.0%**	**0.13 [-0.18, 0.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)

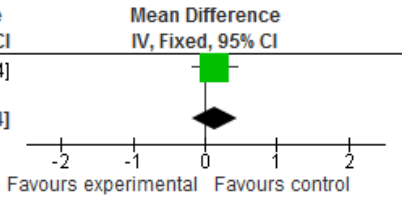


Figure 177: Severe hypoglycaemia less than or equal to 6 months follow-up

Study or Subgroup	Metformin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Meyer 2002	3	31	5	31	100.0%	0.60 [0.16, 2.30]
Total (95% CI)		**31**		**31**	**100.0%**	**0.60 [0.16, 2.30]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)

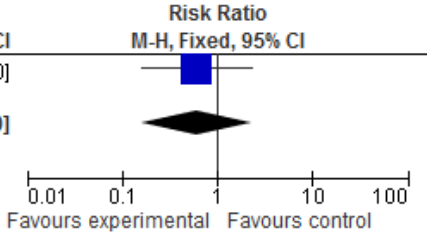


Figure 178: Severe hypoglycaemia more than 6 months follow-up

Study or Subgroup	Metformin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lund 2008	15	49	10	50	100.0%	1.53 [0.76, 3.07]
Total (95% CI)		**49**		**50**	**100.0%**	**1.53 [0.76, 3.07]**
Total events	15		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

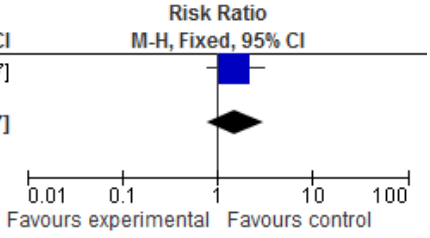


Figure 179: Symptoms of hypoglycaemia less than or equal to 6 months follow-up

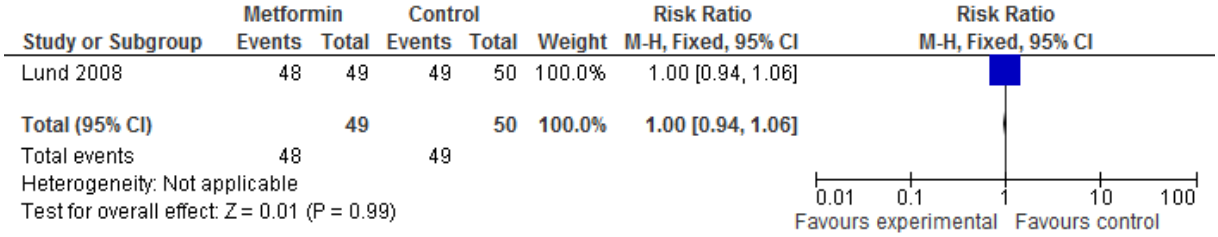


Figure 180: Dose of insulin less than or equal to 6 months follow-up

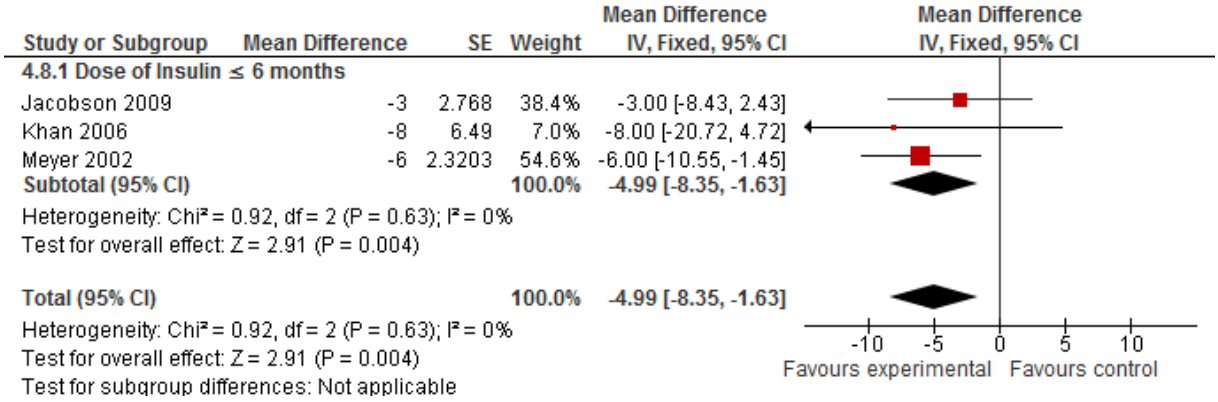


Figure 181: Dose of insulin more than 6 months follow-up

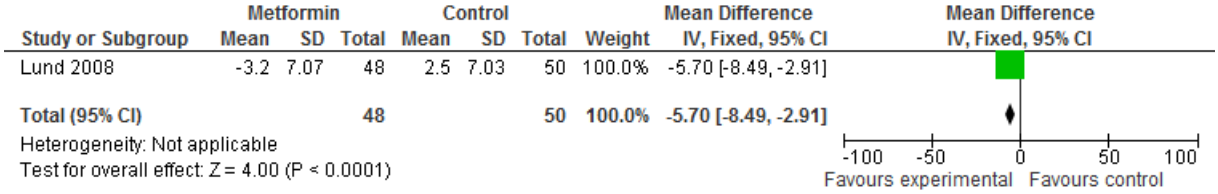


Figure 182: Weight change less than or equal to 6 months follow-up

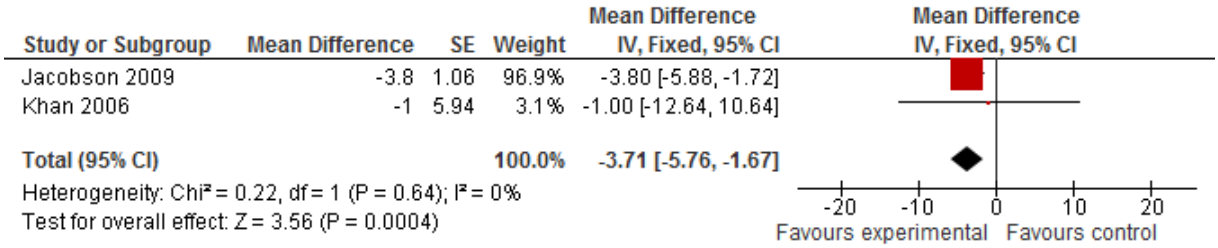


Figure 183: Weight change more than 6 months follow-up

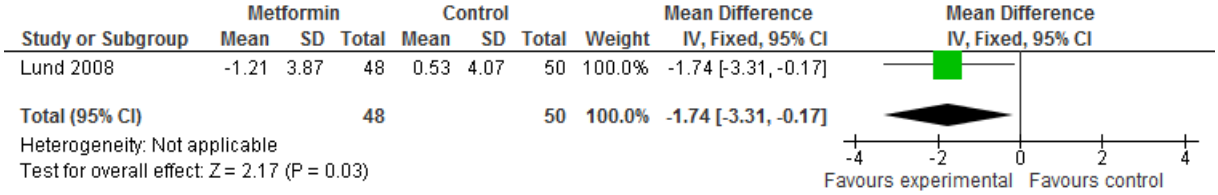


Figure 184: Adverse events - gastrointestinal side effects less than or equal to 6 months follow-up

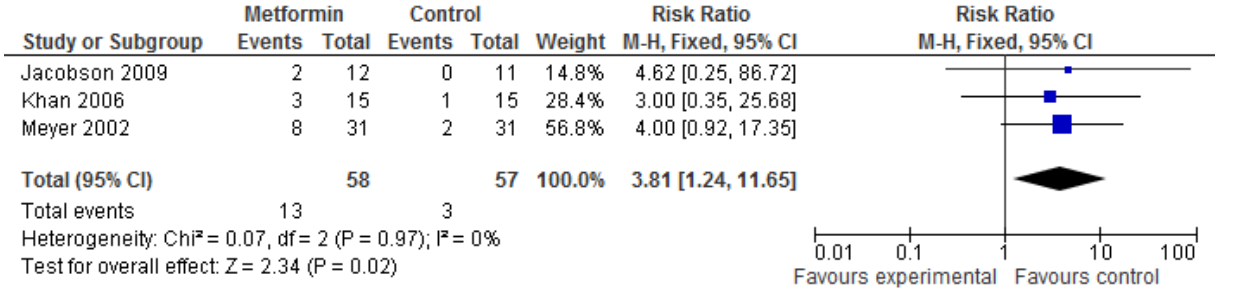


Figure 185: Adverse events - Vomiting less than or equal to 6 months follow-up

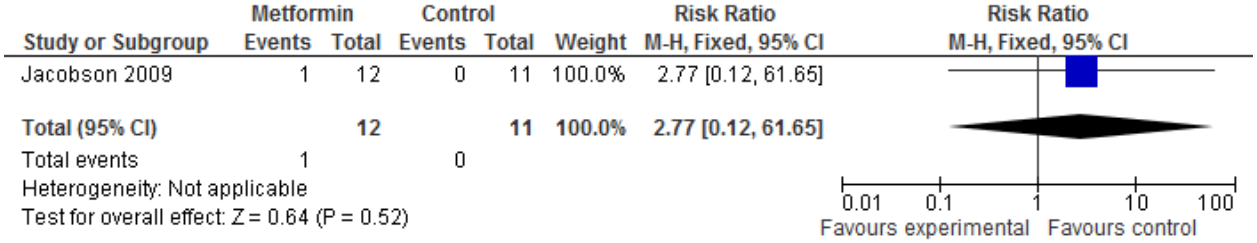
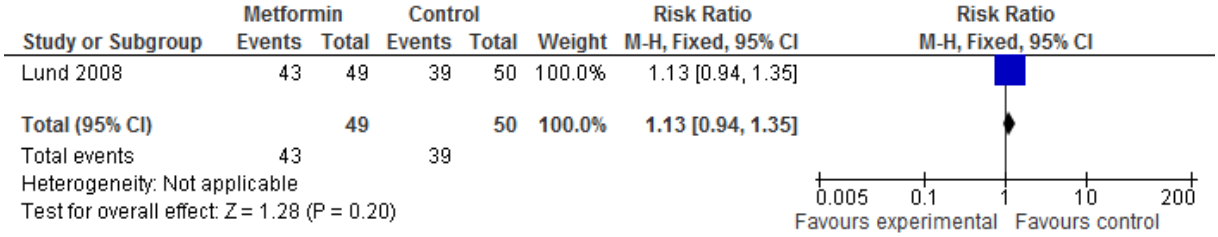


Figure 186: Adverse events - gastrointestinal side effects more than 6 months follow-up

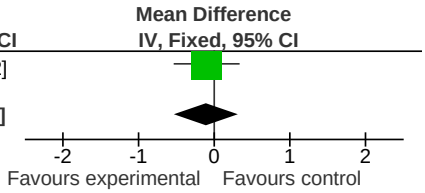


J.4.4.4 Exenatide

Figure 187: HbA1c % less than or equal to 6 months follow-up

Study or Subgroup	Liraglutide Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sarkar 2014	6.6	0.5	13	6.7	0.6	13	100.0%	-0.10 [-0.52, 0.32]
Total (95% CI)			**13**			**13**	**100.0%**	**-0.10 [-0.52, 0.32]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)



Source: *<Insert Source text here>*

Figure 188: Dose of insulin less than or equal to 6 months follow-up

Study or Subgroup	Liraglutide Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pitocco 2013	0.47	0.1	13	0.54	0.13	13	100.0%	-0.07 [-0.16, 0.02]
Total (95% CI)			**13**			**13**	**100.0%**	**-0.07 [-0.16, 0.02]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

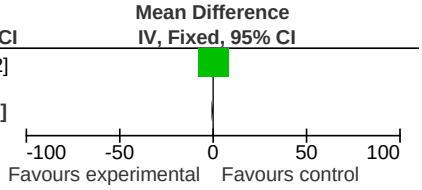
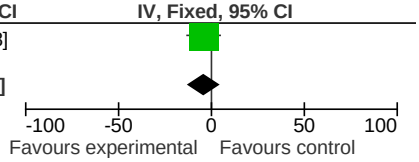


Figure 189: Weight change less than or equal to 6 months follow-up

Study or Subgroup	Liraglutide Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pitocco 2013	72.7	11.8	13	76.9	11.3	13	100.0%	-4.20 [-13.08, 4.68]
Total (95% CI)			**13**			**13**	**100.0%**	**-4.20 [-13.08, 4.68]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)



J.4.5 Once daily basal insulin versus twice daily basal insulin.

Figure 190: HbA1c (%) – Follow-up less than or equal to 6 months

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Follow up ≤ 6 months				
Floch 2009	0.12	0.066327	100.0%	0.12 [-0.01, 0.25]
Subtotal (95% CI)			**100.0%**	**0.12 [-0.01, 0.25]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

Test for subgroup differences: Not applicable

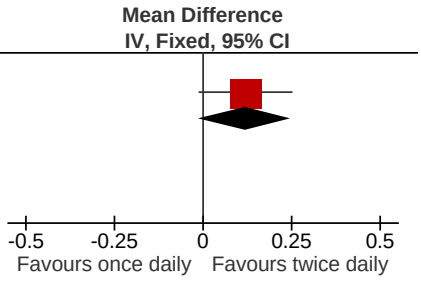
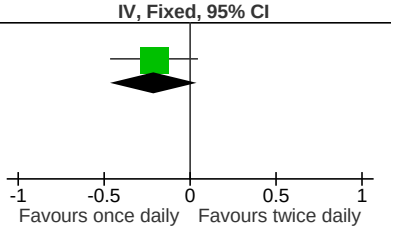


Figure 191: Hypoglycaemia (events per patient per day) – Follow-up less than or equal to 6 months

Study or Subgroup	Once daily Mean	SD	Total	Twice daily Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Follow up ≤ 6 months								
Floch 2009 (1)	1.5	1.14	250	1.71	1.71	262	100.0%	-0.21 [-0.46, 0.04]
Subtotal (95% CI)			**250**			**262**	**100.0%**	**-0.21 [-0.46, 0.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



Test for subgroup differences: Not applicable
(1) Events per patient per day (over 4 months)

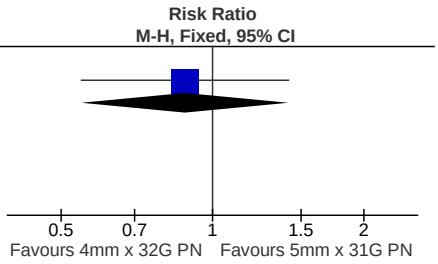
J.4.6 Needle length

J.4.6.1 4 mm (x 32G) PN versus 5 mm (x 31G) PN for insulin delivery.

Figure 192: Hypoglycaemia – Follow up less than or equal to 6 months

Study or Subgroup	4 mm x 32G PN Events	Total	5 mm x 31G PN Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Follow up ≤ 6 months						
Hirsch 2010	36	173	21	89	100.0%	0.88 [0.55, 1.42]
Subtotal (95% CI)		**173**		**89**	**100.0%**	**0.88 [0.55, 1.42]**
Total events	36		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

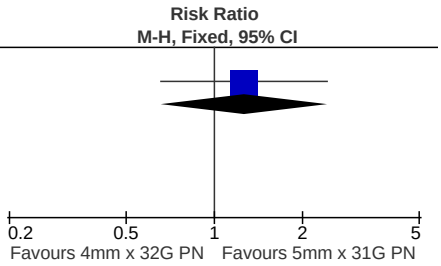


Test for subgroup differences: Not applicable

Figure 193: Injection site pain – Follow up less than or equal to 6 months

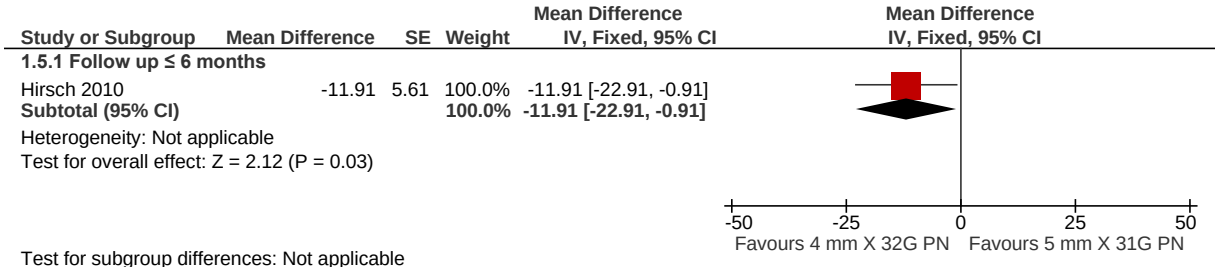
Study or Subgroup	4 mm x 32G PN Events	Total	5 mm x 31G PN Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Follow up ≤ 6 months						
Hirsch 2010	27	173	11	89	100.0%	1.26 [0.66, 2.43]
Subtotal (95% CI)		**173**		**89**	**100.0%**	**1.26 [0.66, 2.43]**
Total events	27		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)



Test for subgroup differences: Not applicable

Figure 194: Visual Analogue Pain Scores – follow up less than or equal to 6 months



J.4.6.2 4 mm x 32G PN versus 8 mm x 31G PN for insulin delivery.

Figure 195: Hypoglycaemia – follow-up less than or equal to 6 months

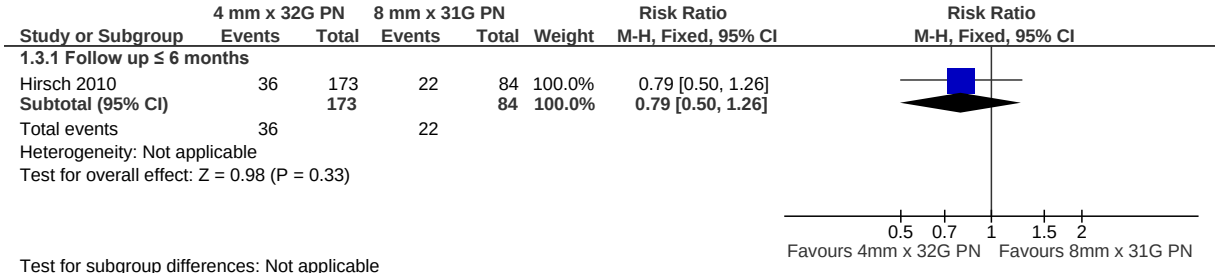


Figure 196: Injection site pain – follow-up less than or equal to 6 months

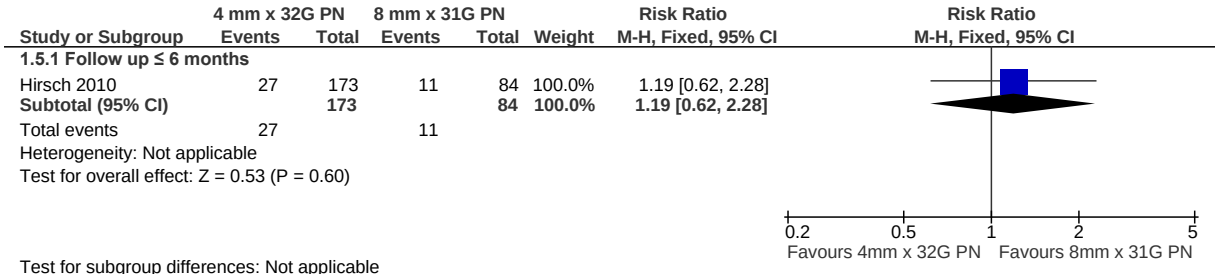
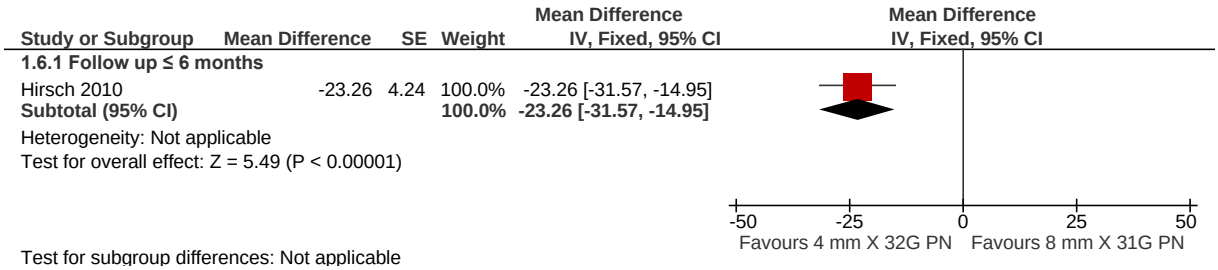
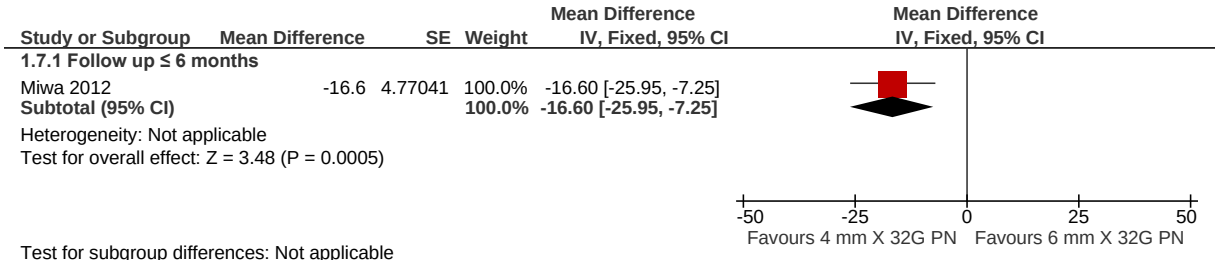


Figure 197: Visual Analogue Pain Scores – follow-up less than or equal to 6 months



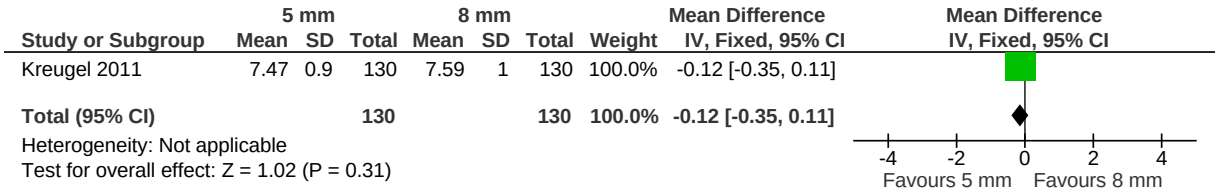
J.4.6.3 4 mm x 32G PN versus 6 mm x 32G PN for insulin delivery.

Figure 198: 150 mm Visual Analogue Scale Pain Scores – follow-up less than or equal to 6 months



J.4.6.4 5 mm versus 8 mm

Figure 199: HbA1c final values – follow-up less than or equal to 6 months



J.5 Pancreas transplant and islet cell transplantation

None

J.6 Hypoglycaemia:

J.6.1 Identification and quantification of impaired awareness of hypoglycaemia

None

J.6.2 Recovering hypoglycaemia awareness

J.6.2.1 Structured education and avoidance (HyPOS) versus education alone in patients with impaired awareness of hypoglycaemia

Figure 200: Hypoglycaemia unawareness: Hypoglycaemia awareness questionnaire (HAQ; Clarke score) less than or equal to 6 months

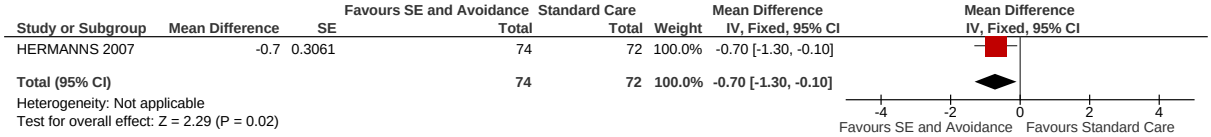


Figure 201: Hypoglycaemia unawareness (Gold score) less than or equal to 6 months

Study or Subgroup	Mean Difference	SE	Education and Avoidance Total	Standard Care Total	Weight	Mean Difference IV, Fixed, 95% CI
HERMANNS 2007	0.8	0.3061	74	72	100.0%	0.80 [0.20, 1.40]
Total (95% CI)			**74**	**72**	**100.0%**	**0.80 [0.20, 1.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)

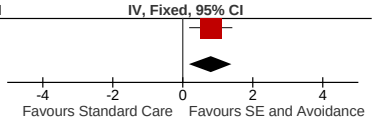


Figure 202: Severe hypoglycaemia (episodes/patient-year) less than or equal to 6 months

Study or Subgroup	Mean Difference	SE	Education and Avoidance Total	Standard Care Total	Weight	Mean Difference IV, Fixed, 95% CI
HERMANNS 2007	-0.3	0.3571	74	72	100.0%	-0.30 [-1.00, 0.40]
Total (95% CI)			**74**	**72**	**100.0%**	**-0.30 [-1.00, 0.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

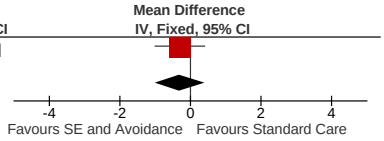


Figure 203: HbA1c %, final values less than or equal to 6 months

Study or Subgroup	Education and Avoidance Mean	SD	Total	Standard Care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
HERMANNS 2007	7.2	0.8	74	7.1	0.9	72	100.0%	0.10 [-0.18, 0.38]
Total (95% CI)			**74**			**72**	**100.0%**	**0.10 [-0.18, 0.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

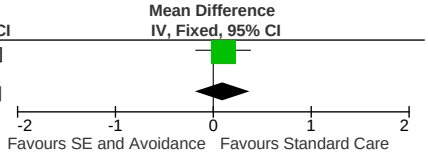


Figure 204: Quality of Life (PAID) less than or equal to 6 months

Study or Subgroup	Mean Difference	SE	Education and Avoidance Total	Standard Care Total	Weight	Mean Difference IV, Fixed, 95% CI
HERMANNS 2007	0.7	1.9898	74	72	100.0%	0.70 [-3.20, 4.60]
Total (95% CI)			**74**	**72**	**100.0%**	**0.70 [-3.20, 4.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

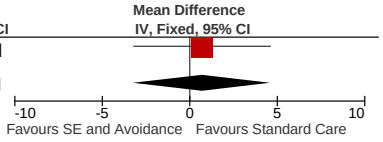
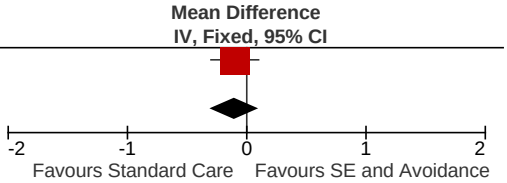


Figure 205: Quality of Life (ADDQoL) less than or equal to 6 months

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
HERMANNS 2007	-0.1	0.102	100.0%	-0.10 [-0.30, 0.10]
Total (95% CI)			**100.0%**	**-0.10 [-0.30, 0.10]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



J.6.2.2 Insulin lispro versus regular human insulin in patients with impaired awareness of hypoglycaemia

Figure 206: Severe hypoglycaemia, number of patients less than or equal to 6 months

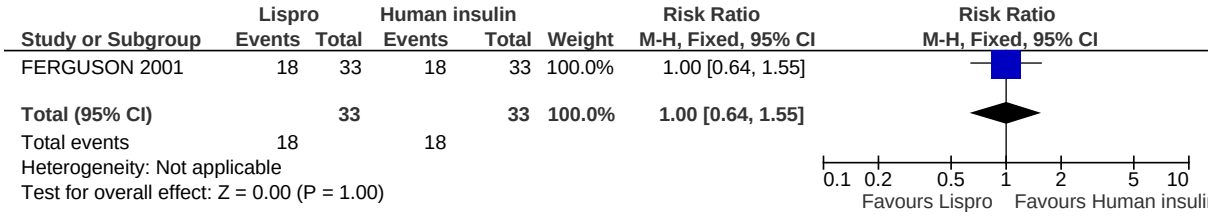
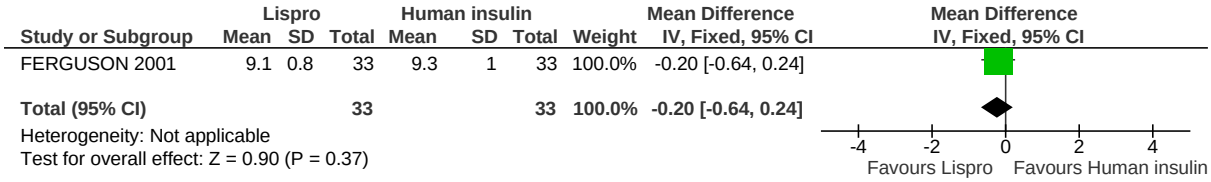


Figure 207: HbA1c %, final values less than or equal to 6 months



J.6.2.3 Education and relaxation of BG targets versus analogue insulin lispro/glargine in patients with impaired awareness of hypoglycaemia

Figure 208: HbA1c % less than or equal to 6 months

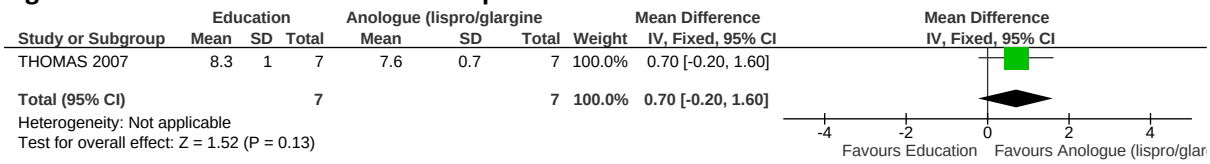


Figure 209: Altered hypoglycaemia awareness, number of patients less than or equal to 6 months

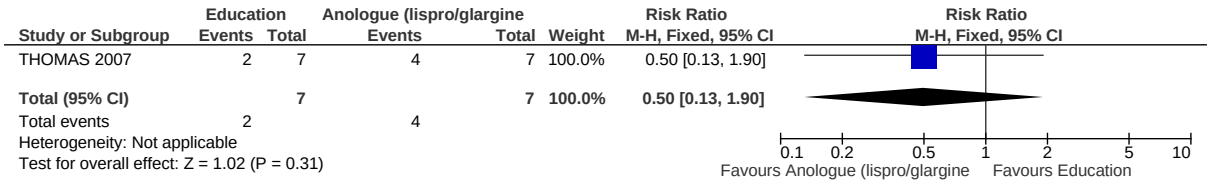


Figure 210: Quality of Life (DQOL) less than or equal to 6 months

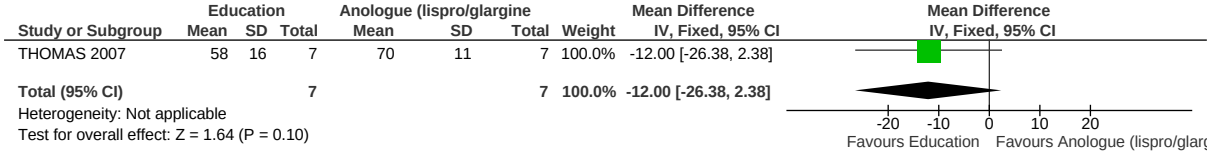
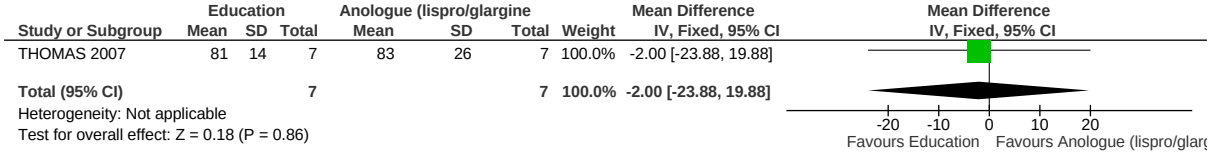


Figure 211: Quality of Life (HFS) less than or equal to 6 months



J.6.2.4 Education and relaxation of BG targets versus CSII in patients with impaired awareness of hypoglycaemia

Figure 212: HbA1c % less than or equal to 6 months

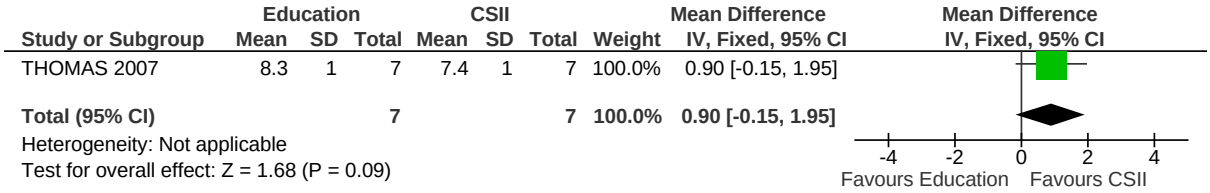


Figure 213: Altered hypoglycaemia awareness, number of patients less than or equal to 6 months

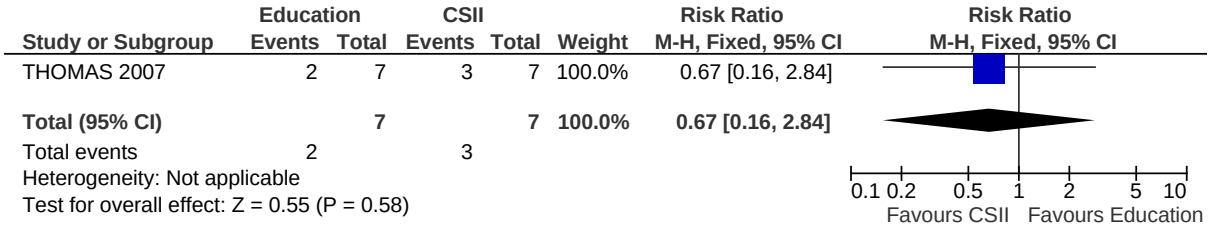


Figure 214: Quality of Life (DQOL) less than or equal to 6 months

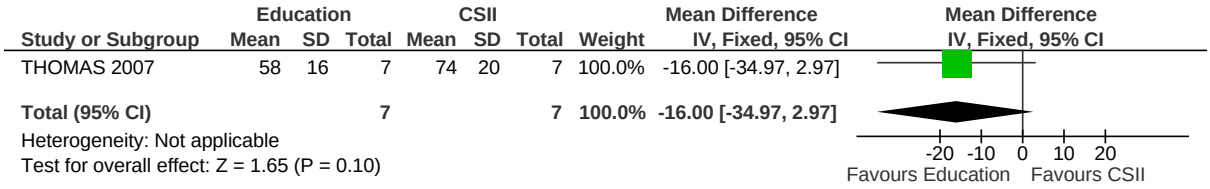
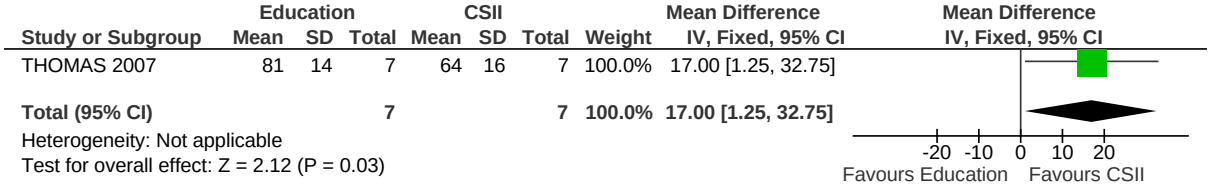


Figure 215: Quality of Life (HFS) less than or equal to 6 months



J.7 Ketone monitoring

J.7.1 Ketone self-monitoring and in-hospital monitoring

J.7.1.1 Blood versus urine ketone measurement (point of care testing) in ED patients (less than or equal to 6 months)

Figure 216: HbA1c

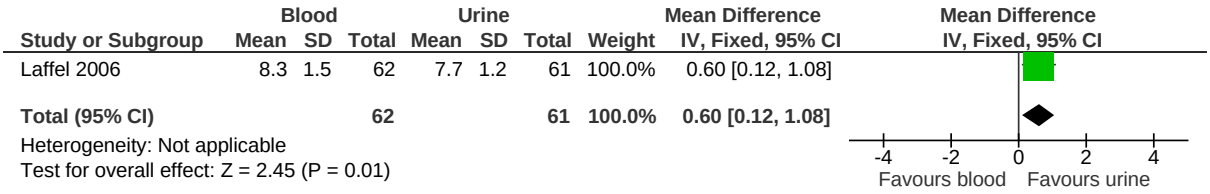


Figure 217: ER use

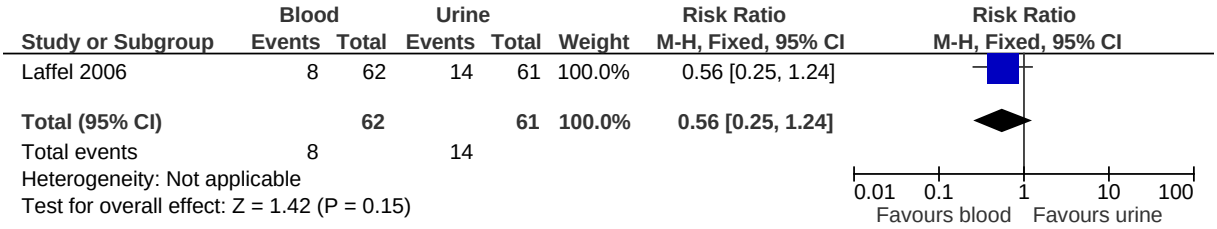
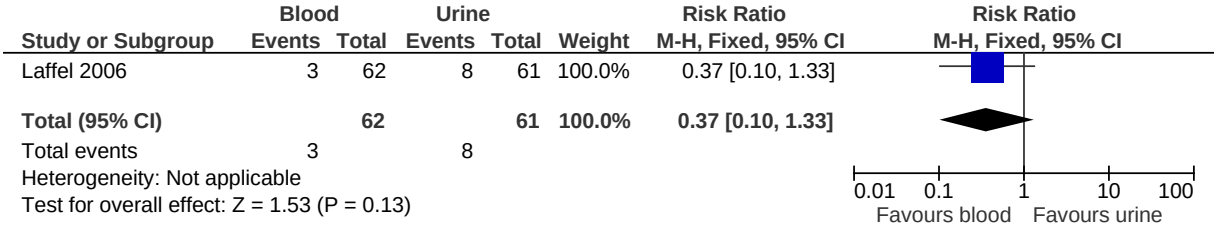


Figure 218: Hospitalisation



J.8 Arterial risk control

J.8.1 Aspirin

J.8.1.1 Aspirin versus placebo for prevention of CV events (less than or equal to 6 months)

Figure 219: HbA1c (aspirin versus placebo in type 1 diabetes)

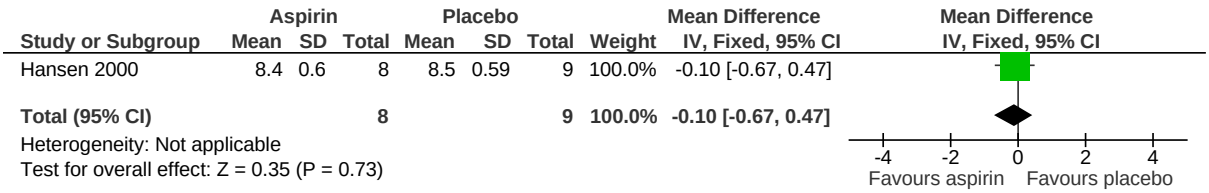
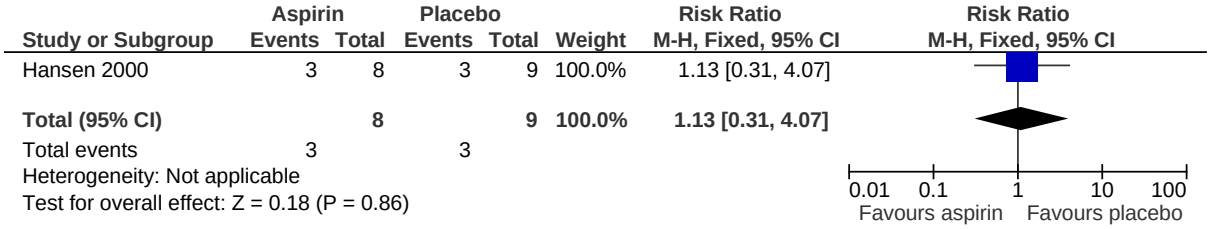


Figure 220: Dyspepsia (aspirin versus placebo in type 1 diabetes)

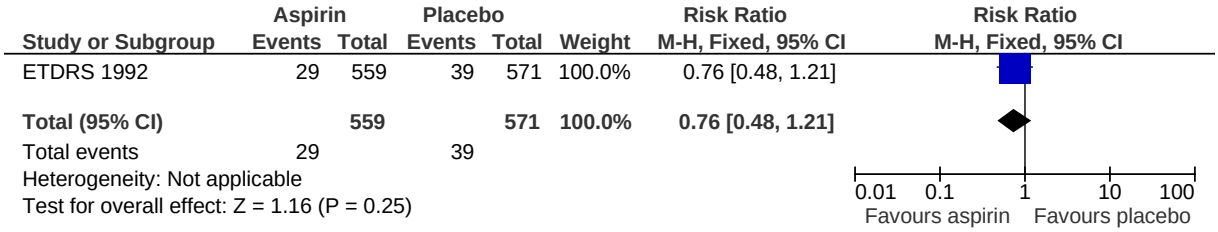


Adverse events (aspirin versus placebo in type 1 diabetes)

No forest plot – data unsuitable

J.8.1.4 Aspirin versus placebo for prevention of CV events (less than or equal to 6 months)

Figure 221: Mortality (all-cause)



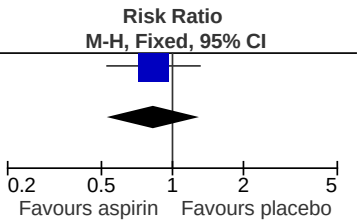
Mortality (all-cause) – 5 year life table

No forest plot – data unsuitable

Figure 222: Mortality (CV)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ETDRS T1D no prev CV	32	683	40	710	100.0%	0.83 [0.53, 1.31]
Total (95% CI)		**683**		**710**	**100.0%**	**0.83 [0.53, 1.31]**
Total events	32		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)



Mortality (CV) – 5 year life table

No forest plot – data unsuitable

Figure 223: CV event (all)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ETDRS T1D no prev CV	55	683	64	710	100.0%	0.89 [0.63, 1.26]
Total (95% CI)		**683**		**710**	**100.0%**	**0.89 [0.63, 1.26]**
Total events	55		64			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

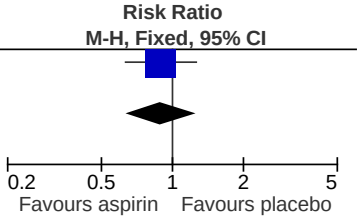
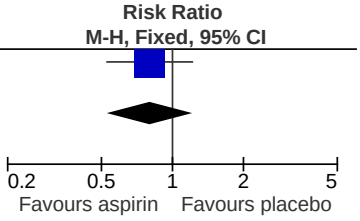


Figure 224: MI (fatal and non-fatal)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ETDRS T1D no prev CV	37	683	48	710	100.0%	0.80 [0.53, 1.21]
Total (95% CI)		**683**		**710**	**100.0%**	**0.80 [0.53, 1.21]**
Total events	37		48			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



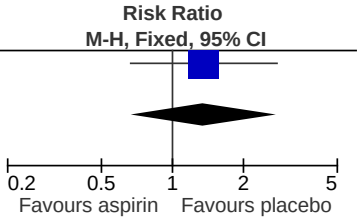
MI (fatal and non-fatal)– 5 year life table

No forest plot – data unsuitable

Figure 225: Stroke (fatal and non-fatal)

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ETDRS T1D no prev CV	17	683	13	710	100.0%	1.36 [0.67, 2.78]
Total (95% CI)		**683**		**710**	**100.0%**	**1.36 [0.67, 2.78]**
Total events	17		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



Stroke (fatal and non-fatal) – 5 year life table

No forest plot – data unsuitable

J.9 Inpatient management

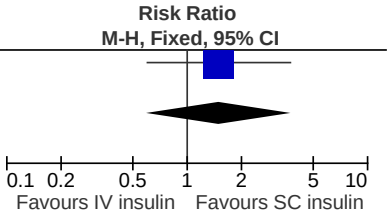
J.9.1 IV insulin

J.9.1.1 IV insulin versus SC insulin during surgery

Figure 226: Mild hypoglycaemia

Study or Subgroup	IV insulin Events	Total	SC insulin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CHRISTIANSEN 1988	6	10	4	10	100.0%	1.50 [0.60, 3.74]
Total (95% CI)		**10**		**10**	**100.0%**	**1.50 [0.60, 3.74]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)



J.10 Complications

J.10.1 Gastroparesis

J.10.1.1 Metoclopramide versus placebo for treatment of gastroparesis (less than 6 months follow-up)

Figure 227: Symptom score, max 100 = worse

Study or Subgroup	Metoclopramide Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
RICCI 1985	26.5	21.6	13	45.3	45.5	13	100.0%	-18.80 [-46.18, 8.58]
Total (95% CI)			**13**			**13**	**100.0%**	**-18.80 [-46.18, 8.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

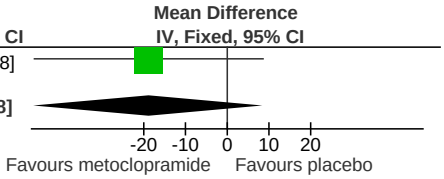


Figure 228: Symptoms – felt better, no. of patients

Study or Subgroup	Metoclopramide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SNAPE 1982	7	10	0	10	100.0%	15.00 [0.97, 231.84]
Total (95% CI)		**10**		**10**	**100.0%**	**15.00 [0.97, 231.84]**
Total events	7		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)

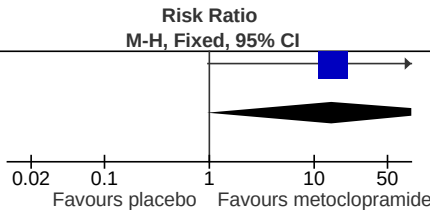


Figure 229: No vomiting, no. of patients

Study or Subgroup	Metoclopramide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SNAPE 1982	6	10	0	10	100.0%	13.00 [0.83, 203.83]
Total (95% CI)		**10**		**10**	**100.0%**	**13.00 [0.83, 203.83]**
Total events	6		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (P = 0.07)

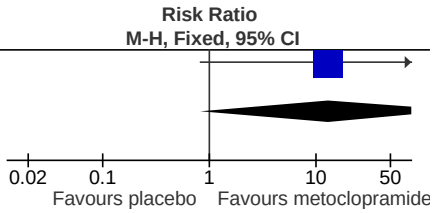


Figure 230: Vomiting, no. of patients improving by score of more than 2

Study or Subgroup	Metoclopramide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
MCCALLUM 1983	6	10	4	8	100.0%	1.20 [0.51, 2.83]
Total (95% CI)		**10**		**8**	**100.0%**	**1.20 [0.51, 2.83]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)

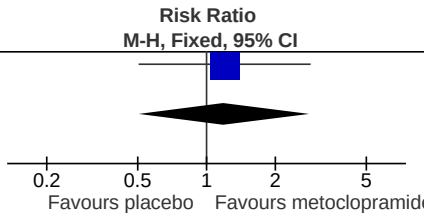


Figure 231: Weight loss, no. of patients

Study or Subgroup	Metoclopramide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SNAPE 1982	3	10	6	10	100.0%	0.50 [0.17, 1.46]
Total (95% CI)		**10**		**10**	**100.0%**	**0.50 [0.17, 1.46]**
Total events	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.21)

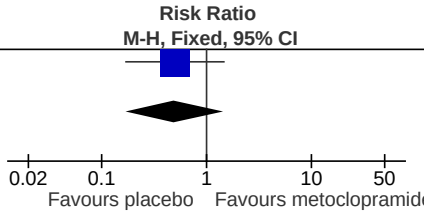
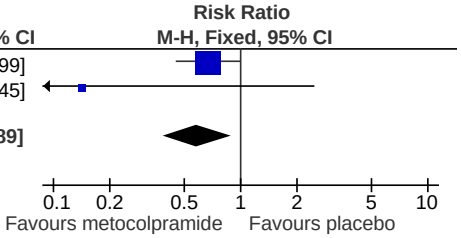


Figure 232: Adverse events, no. of patients

Study or Subgroup	Metoclopramide Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
MCCALLUM 1983	11	18	20	22	83.7%	0.67 [0.45, 0.99]
SNAPE 1982	0	10	3	10	16.3%	0.14 [0.01, 2.45]
Total (95% CI)		**28**		**32**	**100.0%**	**0.59 [0.39, 0.89]**
Total events	11		23			

Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 2.50 (P = 0.01)



J.10.1.2 Domperidone versus placebo for treatment of Gastroparesis (less than 6 months follow-up)

Figure 233: Quality of Life SF-36 – 36 items across 8 domains reduced to 2 (physical and mental components) indexes

Study or Subgroup	Domperidone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Physical Component Scale -Follow up <6 months								
SILVERS 1998	0.65	0.75	104	-1.77	0.75	99	100.0%	2.42 [2.21, 2.63]
Subtotal (95% CI)			**104**			**99**	**100.0%**	**2.42 [2.21, 2.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 22.98 (P < 0.00001)								
1.1.2 Mental Componet Scale -Follow up <6 months								
SILVERS 1998	-1.08	1.13	104	-0.96	0.89	99	100.0%	-0.12 [-0.40, 0.16]
Subtotal (95% CI)			**104**			**99**	**100.0%**	**-0.12 [-0.40, 0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.84 (P = 0.40)								

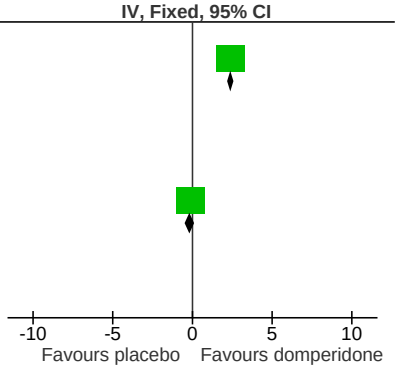


Figure 234: Vomiting

Study or Subgroup	Domperidone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Follow up <6 months						
SILVERS 1998	0	105	5	103	100.0%	0.09 [0.00, 1.59]
Subtotal (95% CI)		**105**		**103**	**100.0%**	**0.09 [0.00, 1.59]**
Total events	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
Test for subgroup differences: Not applicable						

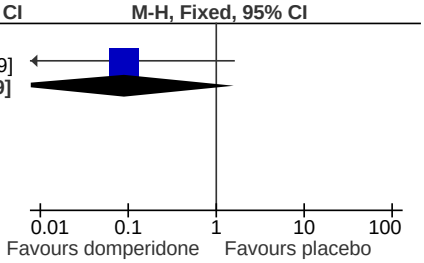


Figure 235: Adverse events

Study or Subgroup	Domperidone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Follow up <6 months						
SILVERS 1998	63	105	65	103	100.0%	0.95 [0.77, 1.18]
Subtotal (95% CI)		**105**		**103**	**100.0%**	**0.95 [0.77, 1.18]**
Total events	63		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Not applicable						

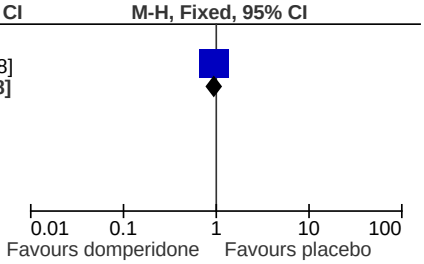
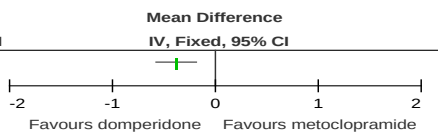


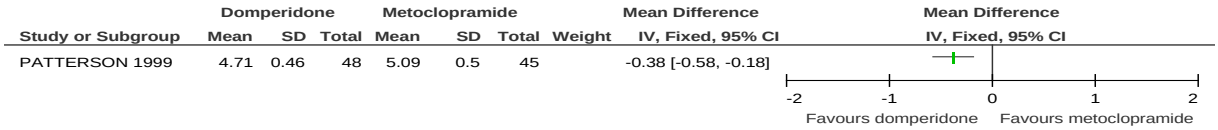
Figure 236: Symptom severity score (maximum 12)

Study or Subgroup	Domperidone Mean	SD	Total	Metoclopramide Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
PATTERSON 1999	4.71	0.46	48	5.09	0.5	45		-0.38 [-0.58, -0.18]



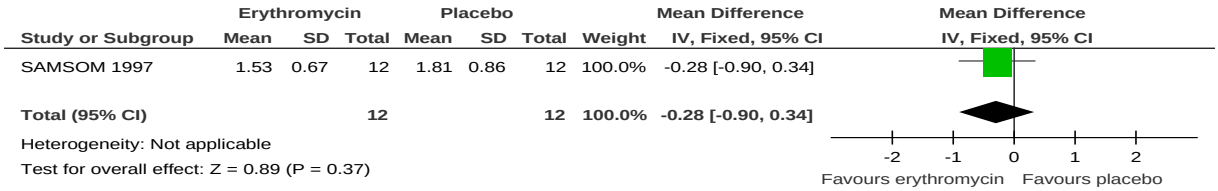
J.10.1.3 Domperidone versus metoclopramide for treatment of gastroparesis (less than 6 months follow-up)

Figure 237: Symptom severity score (maximum 12)



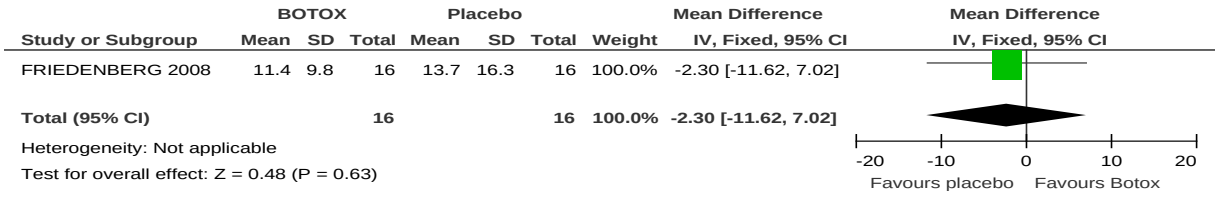
J.10.1.4 Erythromycin versus placebo for treatment of gastroparesis (less than 6 months follow-up)

Figure 238: Symptom severity score (maximum 3.0)



J.10.1.5 BOTOX versus placebo for treatment of gastroparesis (less than 6 months follow-up)

Figure 239: GCSI score reduction (maximum 45)



J.10.1.6 Electrical stimulation ON versus OFF for treatment of gastroparesis (less than 6 months follow-up)

Figure 240: Total symptom severity score (TSS) - 6 symptoms (maximum 24)

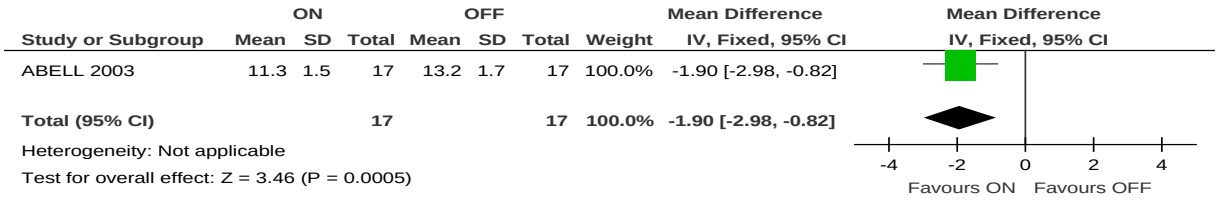


Figure 241: Total symptom severity score (TSS) - 7 symptoms (maximum 28)

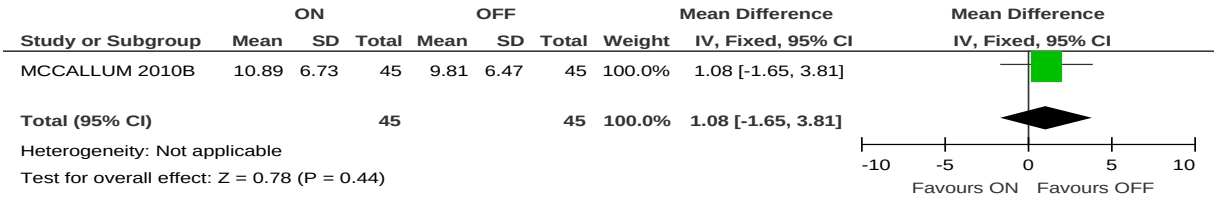


Figure 242: Total symptom frequency score (TSS) - 7 symptoms (maximum 28)

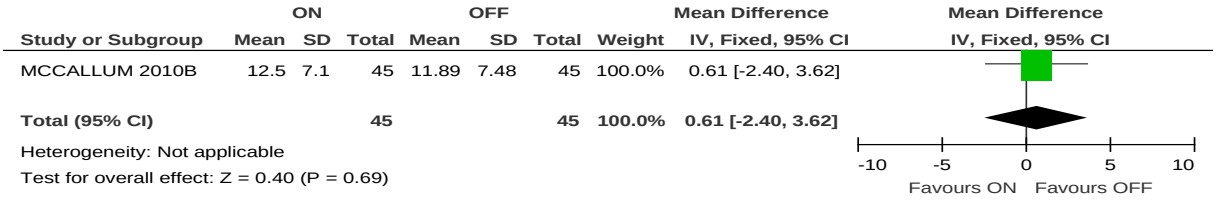


Figure 243: Vomiting severity score (maximum 4)

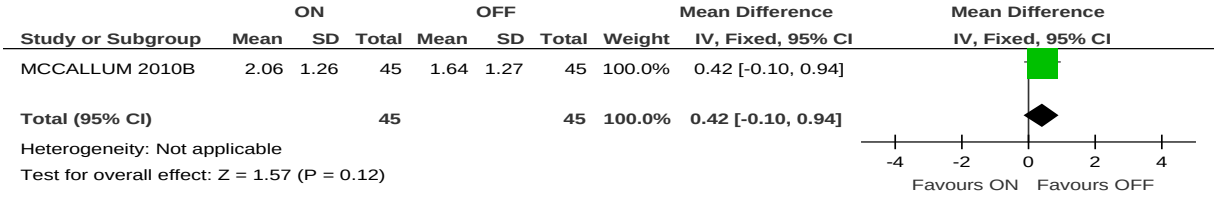


Figure 244: Vomiting frequency (episodes/day)

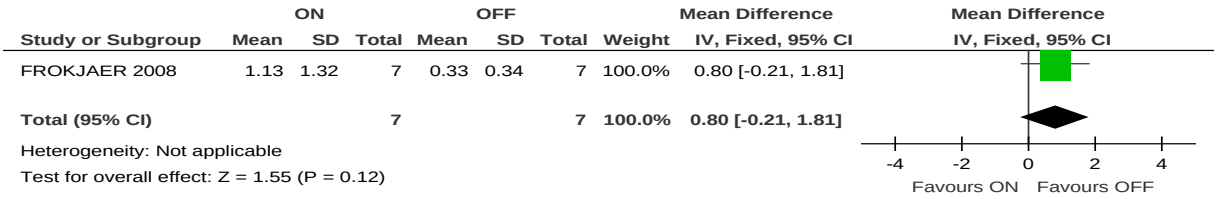
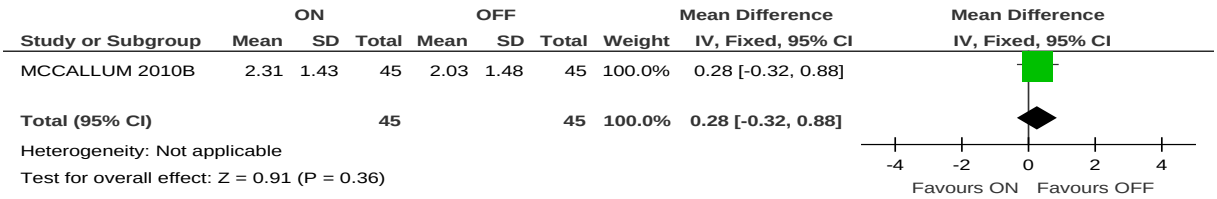


Figure 245: Vomiting frequency score (maximum 4)



J.10.1.7 Small particle diet versus normal diabetic diet for treatment of gastroparesis (less than 6 months follow-up)

Figure 246: HbA1c

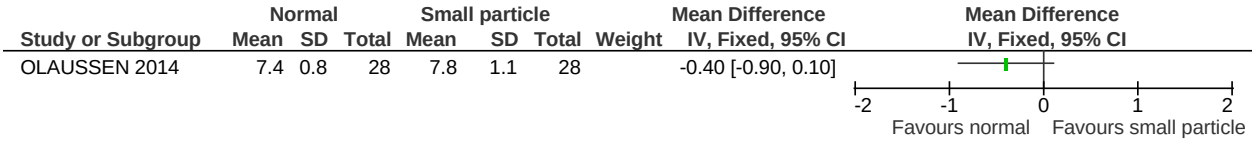


Figure 247: SF-36

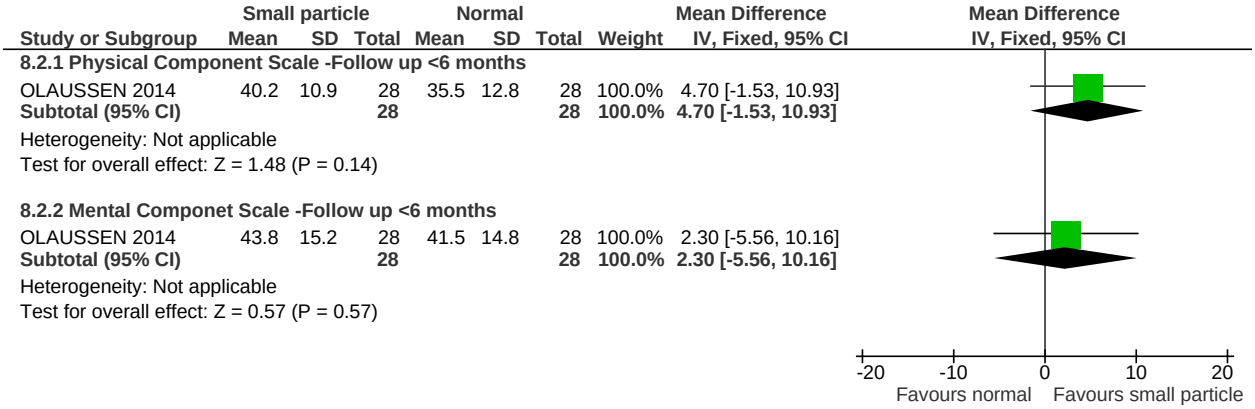


Figure 248: Vomiting/nausea severity

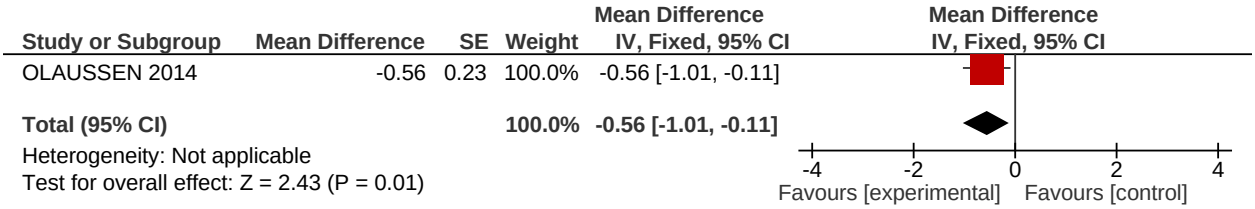
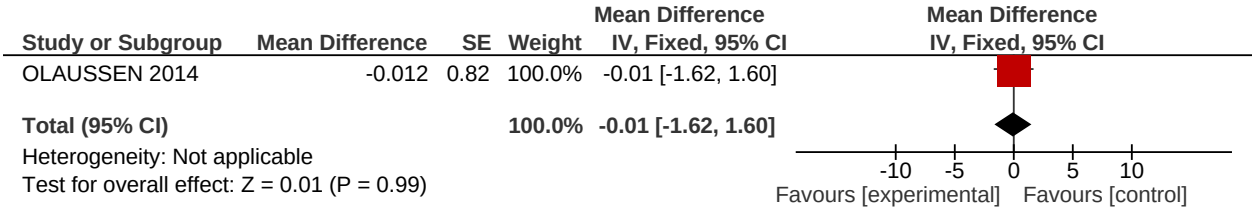


Figure 249: Weight change



J.10.2 Thyroid disease-frequency of monitoring

None

J.10.3 Erectile Dysfunction (type 1 diabetes subgroup analyses only)

For all forest plots used to assess the effectiveness of treatment for erectile dysfunction in men with diabetes (type 1 diabetes and type 2 diabetes) please see NICE clinical guideline for type 2 diabetes, which contains all the review work for this question.

Figure 250: EF domain on IIEF questionnaire for all studies comparing PDE-5 versus placebo showing subgroups by drug comparison for type 1 diabetes only

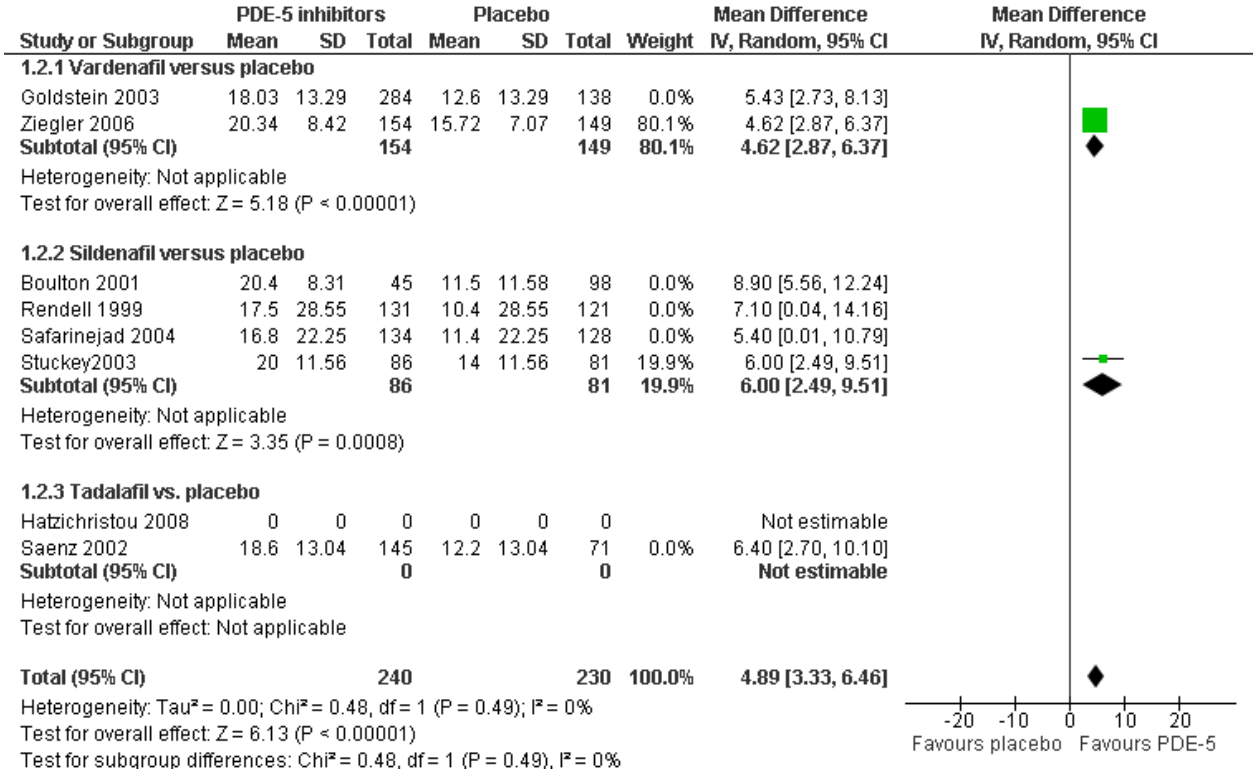


Figure 251: SEP-Q2 (successful penetration) for type 1 diabetes only

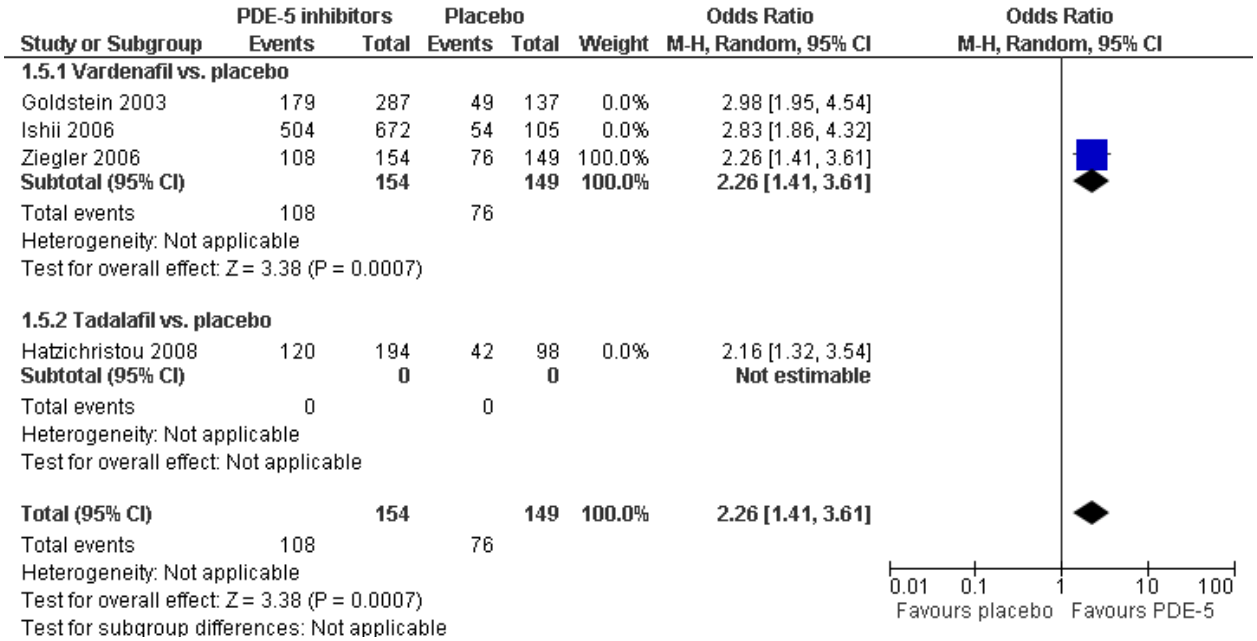


Figure 252: SEP-Q3 (successful intercourse) for type 1 diabetes only

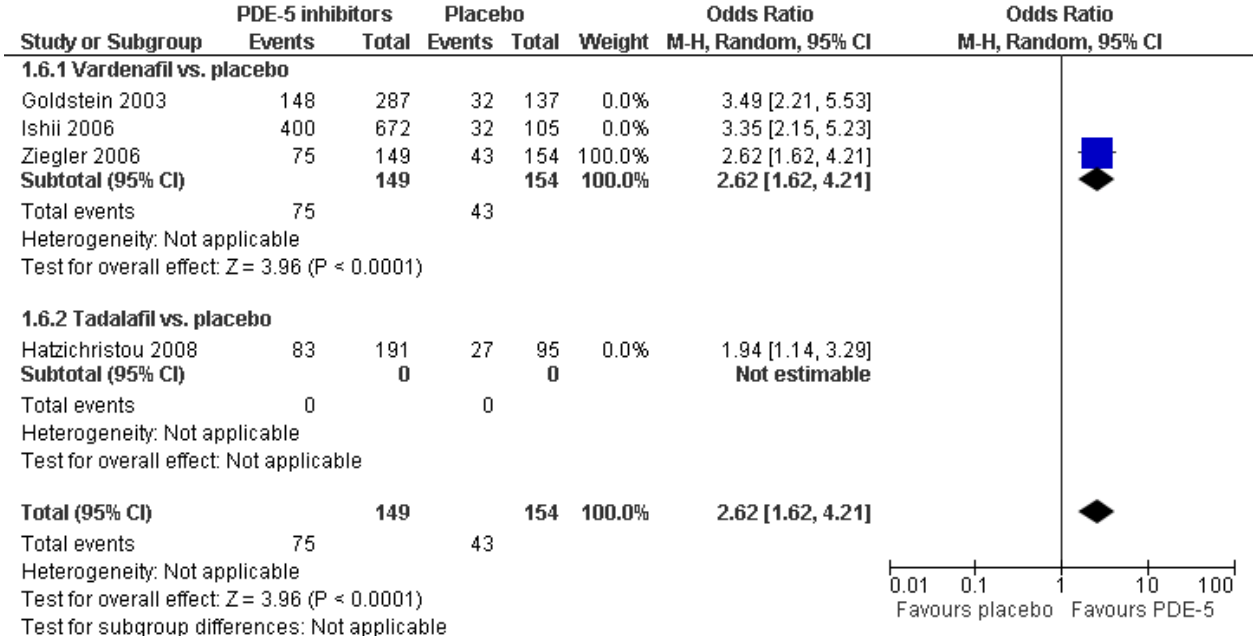


Figure 253: GEQ-improvement for type 1 diabetes only

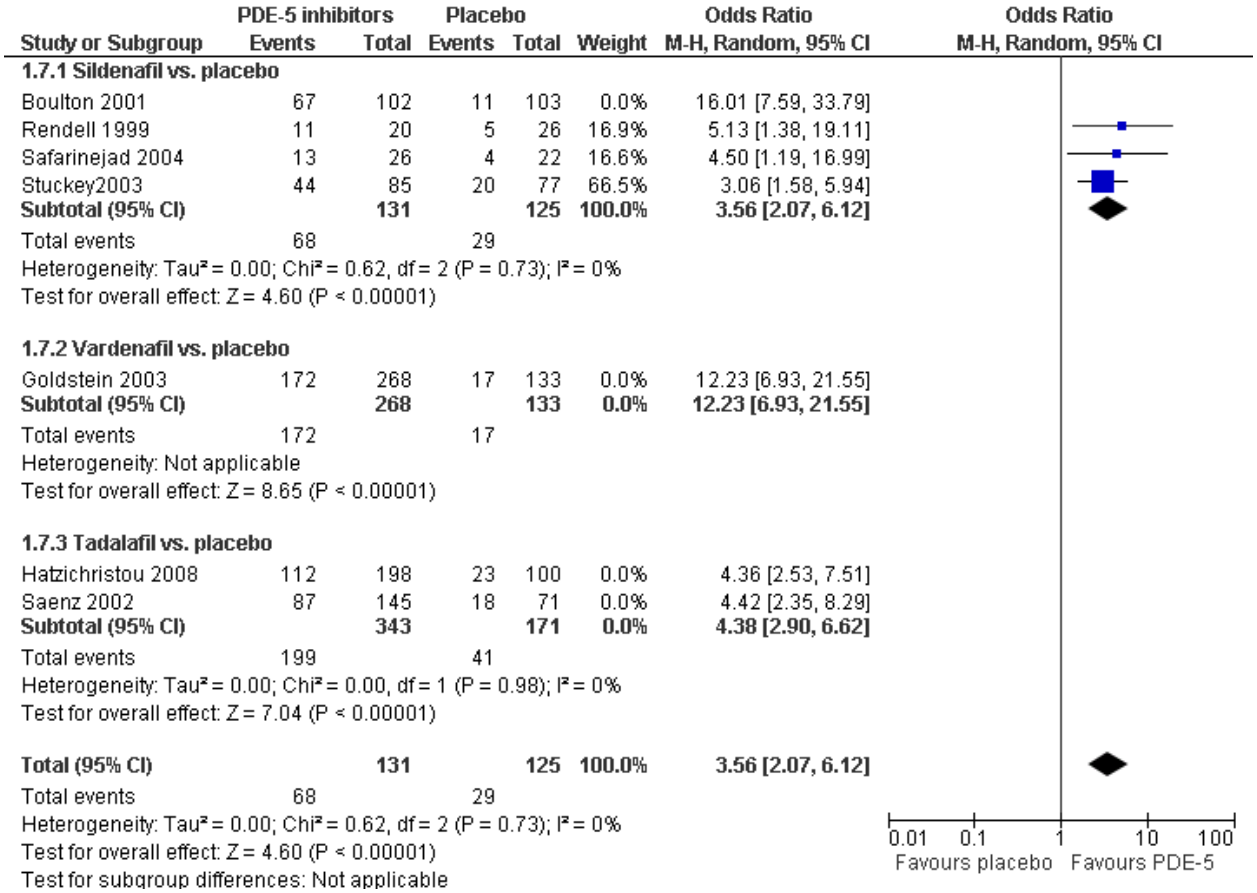
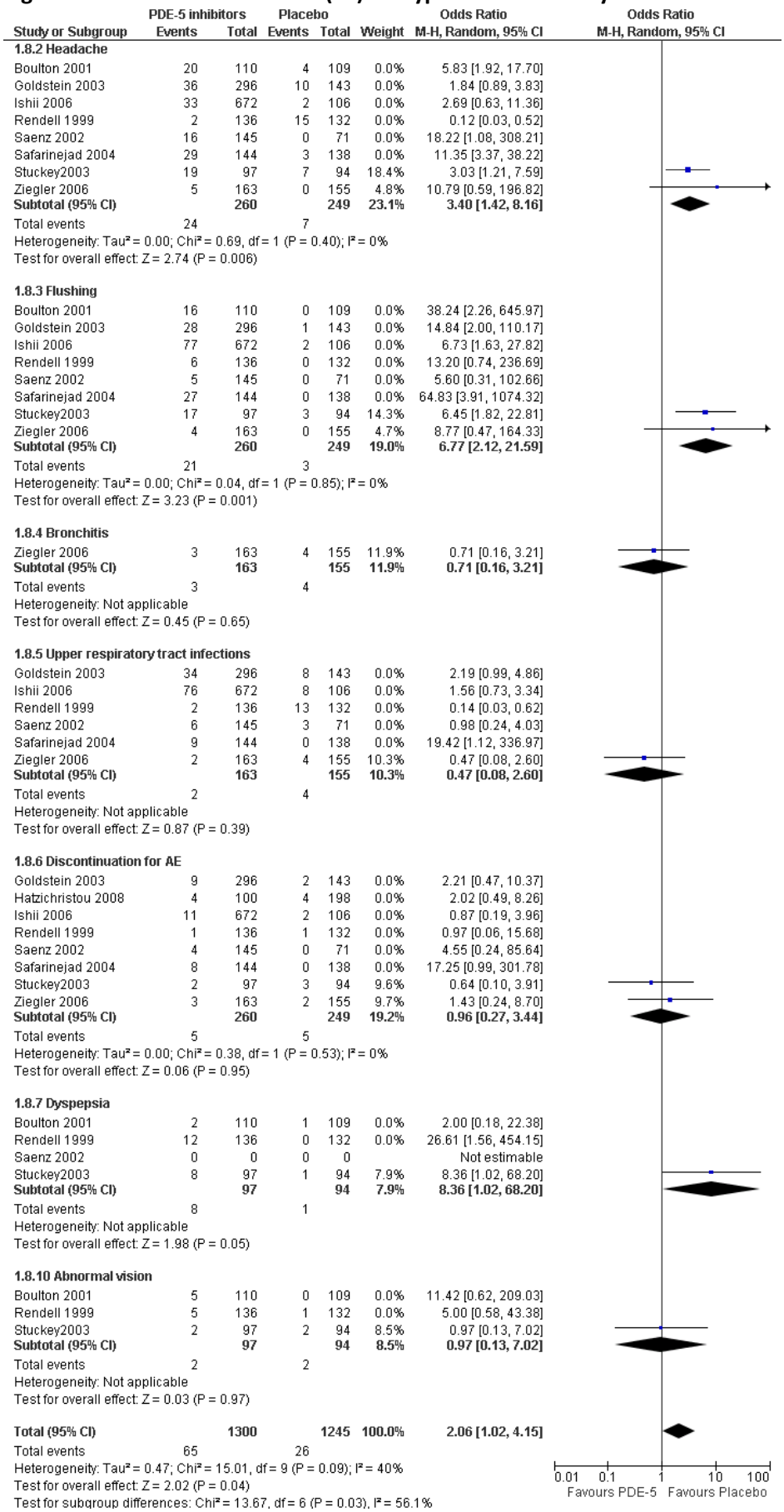


Figure 254: Adverse events (all) for type 1 diabetes only



Appendix K: Excluded clinical studies

Exclusion criteria:

- Studies with mixed population of the following and no subgroup analyses of adults or young people:
  - Children and young people (less than 18 years old)
  - All ages (children, young people and adult)
  - Adults and young people with sample size of n<50 (as we have many studies in adults and adolescents separately already)
- Studies in adults with a sample size of n<50, if there are more than 20 adult studies retrieved.
- Studies in young people with a sample size of n<50, if there are more than 20 young people studies retrieved.
- Studies in children (less than 11 years old)

K.1 Diagnosis

K.1.1 Distinguishing between different types of diabetes

Reference	Reason for exclusion
WENZLAU 2008 J. M. Wenzlau, O. Moua, S. A. Sarkar, L. Yu, M. Rewers, G. S. Eisenbarth, H. W. Davidson, and J. C. Hutton. SlC30A8 is a major target of humoral autoimmunity in type 1 diabetes and a predictive marker in prediabetes. *Ann N Y Acad Sci* 1150:256-259, 2008.	Age of population not reported.
ZMYSLOWSKA 2011 A. Zmyslowska, A. Szadkowska, B. Mianowska, I. Pietrzak, and W. Mlynarski. Association between adiponectin level and residual insulin secretion in type 1 diabetes in children. *Prz.Pediatr.* 41 (2):69-73, 2011.	Not in English
DRETZKE 2004 J. Dretzke, C. Cummins, J. Sandercock, A. Fry-Smith, T. Barrett, and A. Burls. Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus. *Health Technol.Assess.* 8 (22):1-196, 2004.	HTA 2004 in type 1 diabetes children. Wrong markers being assessed: auto-antibodies for celiac and thyroid disease
GALGANI 2012 M. Galgani, R. Nugnes, M. Santopaolo, A. Franzese, S. Formisano, and G. Matarese. Meta-immunological profile of children with type 1 diabetes: Toward the possibility to predict progression of autoimmune diabetes. *Am.J.Pathol.* 181 (3 SUPPL. 1):S11, 2012.	Conference abstract
TAKEDA 2002 H. Takeda, E. Kawasaki, I. Shimizu, E. Konoue, M. Fujiyama, S. Murao, K. Tanaka, K. Mori, Y. Tarumi, I. Seto, Y. Fujii, et al. Clinical, autoimmune, and genetic characteristics of adult-onset diabetic patients with GAD autoantibodies in Japan (Ehime Study). *Diabetes Care* 25 (6):995-1001, 2002.	Wrong population: has not categorised diabetics into the standard different types (including type 1 diabetes, type 2 diabetes) but insulin-deficient and non-insulin deficient.

Reference	Reason for exclusion
BALASUB 2006 A Balasubramanyam, G Garza, L Rodriguez, CS. Hampe, L Gaur, A Lernmark, and MR. Maldonado. Accuracy and predictive value of classification schemes for ketosis-prone diabetes. *Diabetes Care* 29 (12):2575-2579, 2006.	Wrong population: has not categorised diabetics into the standard different types (including type 1 diabetes, type 2 diabetes) but KPD (ketone-prone diabetes) subtypes. Wrong study design: sensitivity and specificity of classification schemes to determine KPD subtypes.
BARKER 2004A JM. Barker, SH. Goehrig, K Barriga, M Hoffman, R Slover, GS. Eisenbarth, JM. Norris, G Klingensmith, M Rewers, and study DAISY. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care* 27 (6):1399-1404, 2004.	Wrong intervention and outcomes: does not look at any of our specified markers.
DABELEA 2011 D. Dabelea, C. Pihoker, J. W. Talton, Jr D'Agostino, W. Fujimoto, G. J. Klingensmith, J. M. Lawrence, B. Linder, S. M. Marcovina, E. J. Mayer-Davis, G. Imperatore, and L. M. Dolan. Etiological approach to characterization of diabetes type: The SEARCH for diabetes in youth study. *Diabetes Care* 34 (7):1628-1633, 2011.	Wrong population: has not categorised diabetics into the standard different types (including type 1 diabetes, type 2 diabetes)
LINDHOLM 2001 E. Lindholm, E. Agardh, T. Tuomi, L. Groop, and C. D. Agardh. Classifying diabetes according to the new WHO clinical stages. *Eur.J.Epidemiol.* 17 (11):983-989, 2001.	Wrong population: has not categorised diabetics into the standard different types (including type 1 diabetes, type 2 diabetes) but insulin-requiring for control (IRC) and non-insulin requiring (NIR).
SORENSON 2010 J. S. Sorensen, F. Vaziri-Sani, F. Pociot, K. Kristensen, C. Brorsson, L. Lyngsoe, B. Dolmer, and N. H. Birkebaek. ZnT8 autoantibody specificities at, and 3-5 years after clinical onset, associates with the age at diagnosis and the SLC30A8 gene polymorphism in Danish children with type 1 diabetes. *Pediatr Diabetes* 11:24, 2010.	Conference abstract
REDONDO 2011 M. J. Redondo, L. M. Rodriguez, M. Escalante, A. Balasubramanyam, and M. Haymond. Forms of pediatric diabetes mellitus defined by antiislet autoimmunity and beta-cell function at diagnosis. *Pediatr Diabetes* 12:98, 2011.	Conference abstract
SEIFERT 2011 K. Seifert, K. Tornow, U. Walschus, H. Kenk, and M. Schlosser. Examination of GAD65 in human serum as a possible marker of ongoing beta cell destruction in autoimmune diabetes. *Diabetologia* 54:S74, 2011.	Conference abstract
HUANG 2010B Z. Huang, Y. Chen, F. Li, and Y. Li. Clinical heterogeneity of type 1 diabetes mellitus at onset. *Diabetologia* 53:S396, 2010.	Conference abstract

Reference	Reason for exclusion
SODERBERGH 2004 A Soderbergh, A Grethe Myhre, O Ekwall, G Gebre-Medhin, H Hedstrand, E Landgren, A Miettinen, P Eskelin, M Halonen et al. Prevalence and clinical associations of 10 defined autoantibodies in autoimmune polyendocrine syndrome type I. *J.Clin.Endocrinol.Metab.* 89 (2):557-562, 2004.	Wrong population: type 1 diabetes with APECED (autoimmune polyendocrinpathy-candidiasis-ectodermal dystrophy)
OAK 2008 S Oak, L K. Gilliam, M Landin-Olsson, C Torn, I Kockum, CR. Pennington, M J. Rowley, MR. Christie, JP Banga, and CS. Hampe. The lack of anti-idiotypic antibodies, not the presence of the corresponding autoantibodies to glutamate decarboxylase, defines type 1 diabetes. Proc.Natl.Acad.Sci.U.S.A. 105 (14):5471-5476, 2008.	Wrong outcomes: not the presence of markers in type 1 diabetes, as recruited pts who were already GAD65+
DEGRAAFF 2007 L. C. G. de Graaff, J. W. A. Smit, and J. K. Radder. Prevalence and clinical significance of organ-specific autoantibodies in type 1 diabetes mellitus. *Neth.J.Med.* 65 (7):235-247, 2007.	Wrong intervention and outcomes: does not look at any of our specified markers.
HATHOUT 2003 EH. Hathout, N Hartwick, OR. Fagoaga, AR Colacino, J Sharkey, M Racine, S Nelsen-Cannarella, and JW. Mace. Clinical, autoimmune, and HLA characteristics of children diagnosed with type 1 diabetes before 5 years of age. *Pediatrics* 111 (4 Pt 1):860-863, 2003.	Wrong population: children <12 years old (both early and later childhood onset)
THUMER 2010 L Thumer, K Adler, E Bonifacio, F Hofmann, M Keller, C Milz, A Munte, and A Gabriele Ziegler. German new onset diabetes in the young incident cohort study: DiMelli study design and first-year results. *Rev.diabet.stud.* 7 (3):202-208, 2010.	Wrong population: children and young people
ALABASI 2003 A. J. Al Abbasi and F. A. Al Jenaidi. Frequency of auto-antibodies in newly diagnosed Bahraini type I diabetes mellitus children and their healthy siblings. *J.Bahrain Med.Soc.* 15 (1):9-12, 2003.	Wrong population: children 1-13 years old.
DESAI 2008 M. Desai and A. Clark. Autoimmune diabetes in adults: lessons from the UKPDS. *Diabet.Med.* 25 Suppl 2:30-34, 2008.	Literature review
VAN DEUTEKOM 2008 A. W. van Deutekom, R. J. Heine, and S. Simsek. The islet autoantibody titres: their clinical relevance in latent autoimmune diabetes in adults (LADA) and the classification of diabetes mellitus. *Diabet.Med.* 25 (2):117-125, 2008.	Literature review
JENSEN 2007 R. Jensen, L. Gilliam, C. Torn, M. Landin-Olsson, J. Palmer, K. Akesson, I. Kockum, B. Lernmark, A. F. Karlsson, K. F. Lynch, N. Breslow, A. Lernmark, G. Sundkvist, and Diabetes Incidence Study in Sweden group. Islet cell autoantibody levels after the diagnosis of young adult diabetic patients.	Wrong population: shows changes in markers over time but does not categorise the diabetes population into different types of diabetes.

Reference	Reason for exclusion
Diabet.Med. 24 (11):1221-1228, 2007.	
ALLEN 2008 S. Allen, J. Huber, and D. Devendra. Prevalence of organ-specific autoantibodies in childhood- and adult-onset type 1 diabetes. *Ann.N.Y.Acad.Sci.* 1150:260-262, 2008.	Wrong markers being assessed:
KOBAYASHI 2006 T. Kobayashi, S. Tanaka, N. Harii, K. Aida, H. Shimura, M. Ohmori, M. Kanesige, A. Shimada, and T. Maruyama. Immunopathological and genetic features in slowly progressive insulin-dependent diabetes mellitus and latent autoimmune diabetes in adults. *Ann.N.Y.Acad.Sci.* 1079:60-66, 2006.	Literature review
LOW 2012 JC. Low, EI. Felner, AB. Muir, M Brown, M Dorcelet, L Peng, and G E. Umpierrez. Do obese children with diabetic ketoacidosis have type 1 or type 2 diabetes? *Prim Care Diabetes* 6 (1):61-65, 2012.	Wrong outcomes: pools together results for Islet cell Abs and GAD Abs so can't separate the two.
LEE 2005 BW Lee, SY Kim, JY Kim, KY Cho, YJ Chung, YK Min, JH Chung, MK Lee, MS Lee, and KW Kim. Heterogeneity of early-onset and ketosis-resistant diabetes in Korean subjects--is it possible to determine cut-off age of early-onset type 2 diabetes? *Diabetes Res.Clin.Pract.* 70 (1):38-45, 2005.	Wrong population: unclear – just says 'early onset diabetes'
MAHON 2009 JL. Mahon, JM. Sosenko, L Rafkin-Mervis, H Krause-Steinrauf, JM. Lachin, C Thompson, PJ. Bingley, E Bonifacio, JP. Palmer, GS. Eisenbarth, J Wolfsdorf, JS. Skyler, TrialNet Natural History Committee, and Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. *Pediatr Diabetes* 10 (2):97-104, 2009.	Wrong outcomes: does not give Ab results for the type 1 diabetes pts; this is just the screening and baseline risk assessment paper. Wrong study population and design – presence of Abs in relatives and see if predicts development of diabetes.
LI 2005 X Li, Z Zhou, G Huang, H Su, X Yan, and L Yang. Metabolic syndrome in adult-onset latent autoimmune diabetes. *Metab.syndr.relat.disord.* 3 (2):174-180, 2005.	Wrong outcomes: prevalence of metabolic syndrome (pts already divided into GAD+ and GAD- .
QUINTANA 2003 FJ. Quintana, G Getz, G Hed, E Domany, and IR. Cohen. Cluster analysis of human autoantibody reactivities in health and in type 1 diabetes mellitus: a bio-informatic approach to immune complexity. *J.Autoimmun.* 21 (1):65-75, 2003.	Wrong interventions and outcomes: different assays/quantification of various markers in antigen clusters.
NAGATA 2004 M Nagata, R Kotani, H Moriyama, K Yokono, BO. Roep, and M Peakman. Detection of autoreactive T cells in type 1 diabetes using coded autoantigens and an immunoglobulin-free cytokine ELISPOT assay: report from the fourth immunology of diabetes society T cell workshop. *Ann.N.Y.Acad.Sci.* 1037:10-15, 2004.	Wrong interventions and outcomes: testing different assays and antibody types for GAD65.

Reference	Reason for exclusion
BROPHY 2011A S. Brophy, H. Davies, G. Dunseath, J. W. Stephens, J. Platts, H. Lane, C. Beaverstock, L. Wakeman, I. Russell, M. Williams, and D. R. Williams. Experience of the introduction of routine antibody testing in primary care and of running a trial for latent autoimmune diabetes in adults (LADA). *Diabetes Res.Clin.Pract.* 93 (1):e49-e52, 2011.	Age of population not given for the main group recruited.
ORTQVIST 2010 E. Ortqvist, B. Brooks-Worrell, K. Lynch, J. Radtke, L. M. Bekris, I. Kockum, C. D. Agardh, C. M. Cilio, A. L. Lethagen, B. Persson, A. Lernmark, J. Reichow, S. Oak, J. P. Palmer, and C. S. Hampe. Changes in GAD65Ab-specific antiidiotypic antibody levels correlate with changes in C-peptide levels and progression to islet cell autoimmunity. *J.Clin.Endocrinol.Metab.* 95 (11):E310-E318, 2010.	Adult patients were treated with anti-GADA and so this study is about treatment effect.
MAUVAIS 2004 F Mauvais-Jarvis, E Sobngwi, R Porcher, JP Riveline, JP Kevorkian, C Vaisse, G Charpentier, PJ Guillausseau, P Vexiau, and JF Gautier. Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. *Diabetes* 53 (3):645-653, 2004.	Adult patients but results divided into ketosis-prone and non-ketosis prone pts.
ROGOWICZ 2012 A. Rogowicz-Frontczak, D. Zozulinska-Ziolkiewicz, P. Niedzwiecki, M. Litwinowicz, and B. Wierusz-Wysocka. Does glucagon stimulation test help to predict autoimmunity in newly diagnosed non obese adults with diabetes? *Exp.Clin.Endocrinol.Diabetes* 120 (7):428-434, 2012.	Type of diabetes population unspecified.
LITTORIN 2003 B. Littorin, L. Nystrom, B. Gullberg, L. Rastam, J. Ostman, H. J. Arnqvist, E. Bjork, G. Blohme, J. Bolinder, J. W. Eriksson, B. Schersten, and G. Sundkvist. Increasing body mass index at diagnosis of diabetes in young adult people during 1983-1999 in the Diabetes Incidence Study in Sweden (DISS). *J.Intern.Med.* 254 (3):251-256, 2003.	Does not give the % of marker in each type of diabetes.
PORKSEN 2010 S Porksen, LB Laborie, L Nielsen, MLM Andersen, T Sandal, H de Wet, E Schwarcz, J Aman, P Swift, M Kocova, EJ. Schonle, C de Beaufort, P Hougaard, F Ashcroft, A Molven, Ml Knip, HB. Mortensen, L Hansen, PR. Njolstad, and Hyidore Study Group on Childhood Diabetes. Disease progression and search for monogenic diabetes among children with new onset type 1 diabetes negative for ICA, GAD- and IA-2 Antibodies. *BMC Endocrine Disorders* 10:16, 2010.	Does not give results for each of the markers separately.
BILGIC 2008 S. Bilgic, E. Aktas, F. Salman, G. Ersahin, G. Erten, M. T. Yilmaz, and G. Deniz. Intracytoplasmic cytokine levels and neutrophil functions in early clinical stage of type 1 diabetes. *Diabetes Res.Clin.Pract.* 79 (1):31-36, 2008.	Wrong markers
KHALANGOT 2009 M. Khalangot, V. Kravchenko, M. Tronko, and V. Gur'ianov. Correlation between the prevalence of type 1 diabetes with the daily insulin dose and	Wrong markers

Reference	Reason for exclusion
the autoimmune process against glutamic acid decarboxylase in adults. *EUR.J.INTERN.MED.* 20 (6):611-615, 2009.	
LUTGENS 2008 MWMD. Lutgens, M Meijer, B Peeters, ML Poulsen, MJ. Rutten, ML. Bots, GJMG. van der Heijden, and SS. Soedamah-Muthu. Easily obtainable clinical features increase the diagnostic accuracy for latent autoimmune diabetes in adults: an evidence-based report. *Prim Care Diabetes* 2 (4):207-211, 2008.	Clinical screening tool for LADA but does nut use our pre-specified markers.
RUBIO 2009 O. Rubio-Cabezas, E. L. Edghill, J. Argente, and A. T. Hattersley. Testing for monogenic diabetes among children and adolescents with antibody-negative clinically defined Type 1 diabetes. *Diabet.Med.* 26 (10):1070-1074, 2009.	Results are split into different genotypes of type 1 diabetes, but not show the markers in each genotype.
ZORENA 2008 K. Zorena, J. Mysliwska, M. Mysliwiec, and A. Balcerska. Analysis of levels of angiogenin in children and adolescents with type 1 diabetes mellitus in relation to the duration of the disease. *Int.Rev.Allergol.Clin.Immunol.* 14 (3-4):98-100, 2008.	Wrong markers
MAKINEN 2008 A Makinen, T Harkonen, J Ilonen, M Knip, and Diabetes Register Finnish Pediatric. Characterization of the humoral immune response to islet antigen 2 in children with newly diagnosed type 1 diabetes. *European journal of endocrinology* 159 (1):19-26, 2008.	Results of patients categorised into responders and nn-responders to single of combination of markers. And specifically recruited pts of IA-2A negative type 1 diabetes.
BROOKS 2011 BM. Brooks-Worrell, JL. Reichow, A Goel, H Ismail, and JP. Palmer. Identification of autoantibody-negative autoimmune type 2 diabetic patients. *Diabetes Care* 34 (1):168-173, 2011.	Results of pts categorised into T-cell + and – and combination of all 5 markers, rather than each marker separately.
KATULANDA 2008 P. Katulanda, B. Shine, G. W. Katulanda, A. Silva, E. L. Asfir, R. Sheriff, N. Somasundaram, A. E. Long, P. J. Bingley, M. I. McCarthy, A. Clark, and D. R. Matthews. Diabetes mellitus among young adults in Sri Lanka--role of GAD antibodies in classification and treatment: the Sri Lanka Young Diabetes study. *Diabetologia* 51 (8):1368-1374, 2008.	Wrong population: mixtuire of type 1 diabetes, type 2 diabetes and LADA with no subgroup analyses for each of these. And further divided into GAD- and GAD+.
FOURLANOS 2006 S Fourlanos, C Perry, MS. Stein, J Stankovich, LC. Harrison, and PG. Colman. A clinical screening tool identifies autoimmune diabetes in adults. *Diabetes Care* 29 (5):970-975, 2006.	Risk scores which do not include our pre-specified markers.
BOLINDER 2005 J. Bolinder, P. Fernlund, H. Borg, H. J. Arnqvist, E. Bjork, G. Blohme, J. W. Eriksson, L. Nystrom, J. Ostman, and G. Sundkvist. Hyperproinsulinemia segregates young adult patients with newly diagnosed autoimmune (type 1) and non-autoimmune (type 2) diabetes. *Scand.J.Clin.Lab.Invest.* 65 (7):585-594, 2005.	Wrong markers

Reference	Reason for exclusion
STEELE 2004 C. Steele, W. A. Hagopian, S. Gitelman, U. Masharani, M. Cavaghan, K. I. Rother, D. Donaldson, D. M. Harlan, J. Bluestone, and K. C. Herold. Insulin secretion in type 1 diabetes. *Diabetes* 53 (2):426-433, 2004.	
GABBAYA 2012 M. Andrade Lima Gabbay, M. N. Sato, A. J. S. Duarte, and S. A. Dib. Serum titres of anti-glutamic acid decarboxylase-65 and anti-IA-2 autoantibodies are associated with different immunoregulatory milieu in newly diagnosed type 1 diabetes patients. *Clin.Exp.Immunol.* 168 (1):60-67, 2012.	
GREENBAUM 2012 CJ. Greenbaum, CA. Beam, D Boulware, SE. Gitelman, PA. Gottlieb, KC. Herold, JM. Lachin, P McGee et al., and Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes* 61 (8):2066-2073, 2012.	
SOSENKO 2008A JM. Sosenko, JP. Palmer, L Rafkin-Mervis, JP. Krischer, D Cuthbertson, D Matheson, and JS. Skyler. Glucose and C-peptide changes in the perionset period of type 1 diabetes in the Diabetes Prevention Trial-Type 1. *Diabetes Care* 31 (11):2188-2192, 2008.	
UNNIKRISH 2008 A. G. Unnikrishnan, E. Bhatia, V. Bhatia, S. K. Bhadada, R. K. Sahay, A. Kannan, V. Kumaravel, D. Sarma, B. Ganapathy, N. Thomas, M. John, R. V. Jayakumar, H. Kumar, V. Nair, and C. B. Sanjeevi. Type 1 diabetes versus type 2 diabetes with onset in persons younger than 20 years of age: Results from an Indian multicenter study. *Ann.N.Y.Acad.Sci.* 1150:239-244, 2008.	
AGUILERA 2004 E Aguilera, R Casamitjana, G Ercilla, J Oriola, R Gomis, and I Conget. Adult-onset atypical (type 1) diabetes: additional insights and differences with type 1A diabetes in a European Mediterranean population. *Diabetes Care* 27 (5):1108-1114, 2004.	
RAHA 2011 O. Raha, B. N. Sarkar, L. V. K. S. Bhaskar, P. Veerraju, S. Chowdhury, S. Mukhopadhyay, T. K. Biswas, and V. R. Rao. Insulin (INS) promoter vntr polymorphisms: Interactions and association with type 1 diabetes mellitus in bengali speaking patients of Eastern India. *Diabetol.Croat.* 40 (4):99-106, 2011.	
SERBAN 2004 V. Serban, A. Enache, A. Vlad, Alexandra Sima, Mihaela Rosu, Adriana Rosca, and Carmina Draghici. GADA and islet cell antibodies in Romanian children and adolescents with diabetes mellitus. *Rom.J.Intern.Med.* 42 (2):325-332, 2004.	
TANAKA 2004	

Reference	Reason for exclusion
S Tanaka, T Endo, K Aida, H Shimura, N Yokomori, M Kaneshige, F Furuya, S Amemiya, M Mochizuki, K Nakanishi, and T Kobayashi. Distinct diagnostic criteria of fulminant type 1 diabetes based on serum C-peptide response and HbA1c levels at onset. *Diabetes Care* 27 (8):1936-1941, 2004.	
YANG 2010 L Yang, S Luo, G Huang, J Peng, X Li, X Yan, J Lin, JM. Wenzlau, HW. Davidson, JC. Hutton, and Z Zhou. The diagnostic value of zinc transporter 8 autoantibody (ZnT8A) for type 1 diabetes in Chinese. *Diabetes.Metab.Res.Rev.* 26 (7):579-584, 2010.	
SIRAJ 2012 E. S. Siraj, D. G. Rogers, M. K. Gupta, and S. S. K. Reddy. A Simple Screening Method for Individuals at Risk of Developing Type 1 Diabetes: Measurement of Islet Cell Autoantibodies (GADA, IA-2A, and IAA) on Dried Capillary Blood Spots Collected on Filter Paper. *Horm.Metab.Res.* 44 (11):855-860, 2012.	
MARUYAMA 2008A T Maruyama, S Oak, A Shimada, and CS. Hampe. GAD65 autoantibody responses in Japanese latent autoimmune diabetes in adult patients. *Diabetes Care* 31 (8):1602-1607, 2008.	
DAGDELEN 2009 S. Dagdelen, G. Hascelik, and M. Bayraktar. Simultaneous triple organ specific autoantibody profiling in adult patients with type 1 diabetes mellitus and their first-degree relatives. *Int.J.Clin.Pract.* 63 (3):449-456, 2009.	
HICKEY 2007 D Hickey, G Joshy, P Dunn, D Simmons, and R Lawrenson. Glycaemic control and antibody status among patients with newly diagnosed Type 1 diabetes. *N.Z.Med.J.* 120 (1262):U2732, 2007.	
SCHLOOT 2007A N. C. Schloot, P. Hanifi-Moghaddam, N. Aabenhus-Andersen, B. Z. Alizadeh, M. T. Saha, M. Knip, D. Devendra, T. Wilkin, E. Bonifacio, B. O. Roep, H. Kolb, and T. Mandrup-Poulsen. Association of immune mediators at diagnosis of Type 1 diabetes with later clinical remission. *Diabet.Med.* 24 (5):512-520, 2007.	
SILVA 2003 R. C. Silva, C. Sallorenzo, C. E. Kater, S. A. Dib, and A. Falorni. Autoantibodies against glutamic acid decarboxylase and 21-hydroxylase in Brazilian patients with type 1 diabetes or autoimmune thyroid diseases. *Diabetes Nutr Metab* 16 (3):160-168, 2003.	
NG 2002A W. Y. Ng, Y. S. Lee, A. L. Todd, K. F. Lui, K. Y. Loke, and A. C. Thai. Tyrosine phosphatase-like protein (IA-2) and glutamic acid decarboxylase (GAD65) autoantibodies: a study of Chinese patients with diabetes mellitus. *Autoimmunity* 35 (2):119-124, 2002.	

Reference	Reason for exclusion
KAWASAKI 2011A E Kawasaki, K Nakamura, G Kuriya, T Satoh, M Kobayashi, H Kuwahara, N Abiru, H Yamasaki, N Matsuura, J Miura, Y Uchigata, and K Eguchi. Differences in the humoral autoreactivity to zinc transporter 8 between childhood- and adult-onset type 1 diabetes in Japanese patients. *Clin.Immunol.* 138 (2):146-153, 2011.	
KAWASAKI 2011 E Kawasaki, K Nakamura, G Kuriya, T Satoh, M Kobayashi, H Kuwahara, N Abiru, H Yamasaki, N Matsuura, J Miura, Y Uchigata, and K Eguchi. Zinc transporter 8 autoantibodies in fulminant, acute-onset, and slow-onset patients with type 1 diabetes. *Diabetes.Metab.Res.Rev.* 27 (8):895-898, 2011.	
MARUYAMA 2011 T Maruyama, T Nakagawa, A Kasuga, and M Murata. Heterogeneity among patients with latent autoimmune diabetes in adults. *Diabetes.Metab.Res.Rev.* 27 (8):971-974, 2011.	
LOUET 2008 J. F. Louet, S. B. Smith, J. F. Gautier, M. Molokhia, M. L. Virally, J. P. Kevorkian, P. J. Guillausseau, P. Vexiau, G. Charpentier, M. S. German, C. Vaisse, M. Urbanek, and F. Mauvais-Jarvis. Gender and neurogenin3 influence the pathogenesis of ketosis-prone diabetes. *Diabetes Obes Metab* 10 (10):912-920, 2008.	
BUZZETTI 2007 R Buzzetti, S Di Pietro, A Giaccari, A Petrone, M Locatelli, C Suraci, M Capizzi, M L Arpi, E Bazzigaluppi, F Dotta, E Bosi, and Non Insulin Requiring Autoimmune Diabetes Study Group. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care* 30 (4):932-938, 2007.	Wrong population: age groups not specified
TICA 2003 V Tica, MW Hanif, A Andersson, G. Valsamakis, A. H. Barnett, S Kumar, and C. B. Sanjeevi. Frequency of latent autoimmune diabetes in adults in Asian patients diagnosed as type 2 diabetes in Birmingham, United Kingdom. *Ann.N.Y.Acad.Sci.* 1005:356-358, 2003.	
TIROLO 2009	
SKUPIEN 2008 J. Skupien, S. Gorczynska-Kosiorz, T. Klupa, K. Cyganek, K. Wanic, M. Borowiec, J. Sieradzki, and M. T. Malecki. Molecular background and clinical characteristics of HNF1A MODY in a Polish population. *Diabetes Metab.* 34 (5):524-528, 2008.	
MOREIRA 2011 MC Moreira, GM Lara, R Linden, LR Feksa, R G Tavares, SE de Matos Almeida, and DB Berlese. Frequency of the anti-glutamic acid decarboxylase	Age range of population not specified

Reference	Reason for exclusion
immunological marker in patients with diabetes duration longer than three years in southern Brazil. *Sao Paulo Med J* 129 (3):130-133, 2011.	
PRAZNY 2005 M. Prazny, J. Skrha, Z. Limanova, Z. Vanickova, J. Hilgertova, J. Prazna, M. Jaresova, and I. Striz. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. *Physiol.Res.* 54 (1):41-48, 2005.	Age range of population not specified
XU 2005 Ju Xu, QH Dan, V Chan, NMS. Wat, S Tam, SC Tiu, KF Lee, SC Siu, MW Tsang, L M Fung, KW Chan, and KSL. Lam. Genetic and clinical characteristics of maturity-onset diabetes of the young in Chinese patients. *Eur.J.Hum.Genet.* 13 (4):422-427, 2005.	Age range of population not specified
ANDERSSON 2013 C. Andersson, F. Vaziri-Sani, Aj Delli, B. Lindblad, A. Carlsson, G. Forsander, J. Ludvigsson, C. Marcus, U. Samuelsson, Sa Ivarsson, A. Lernmark, H. Elding Larsson, and BDD Study Group. Triple specificity of ZnT8 autoantibodies in relation to HLA and other islet autoantibodies in childhood and adolescent type 1 diabetes. *Pediatr.Diabetes* 14 (2):97-105, 2013.	FOR CHILDREN/YOUNG PPLE GUIDELINE
SAMUELSSON 2013 U. Samuelsson, B. Lindblad, A. Carlsson, G. Forsander, S. Ivarsson, I. Kockum, A. Lernmark, C. Marcus, J. Ludvigsson, and Better Diabetes Diagnosis study group. Residual beta cell function at diagnosis of type 1 diabetes in children and adolescents varies with gender and season. *Diabetes.Metab.Res.Rev.* 29 (1):85-89, 2013.	FOR CHILDREN/YOUNG PPLE GUIDELINE
ORAM 2014 R. A. Oram, A. G. Jones, R. E. J. Besser, B. A. Knight, B. M. Shields, R. J. Brown, A. T. Hattersley, and T. J. McDonald. The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* 57 (1):187-191, 2014.	FOR CHILDREN/YOUNG PPLE GUIDELINE
DELLI 2012A AJ. Delli, Fariba Vaziri-Sani, Bengt Lindblad, Helena Elding-Larsson, Annelie Carlsson, Gun Forsander, Sten A. Ivarsson, et al. and Better Diabetes Diagnosis study group. Zinc transporter 8 autoantibodies and their association with SLC30A8 and HLA-DQ genes differ between immigrant and Swedish patients with newly diagnosed type 1 diabetes in the Better Diabetes Diagnosis study. *Diabetes* 61 (10):2556-2564, 2012.	Excluded even for children/young pple GL, because doesn't give the actual % of pple (or the titre) who are Ab+ for the young pple or children's subgroup.
ALI 2012 N. A. Ali, E. Swelam, E. A. Al Banna, and A. Showkry. Role of beta-cell autoantibodies as a predictor marker in diabetic patients and their relationship to glycemic control. *Egyptian journal of immunology/Egyptian Association of Immunologists* 19 (1):39-49, 2012.	Adults and children mixed population – but adult subgroup analysis. Adult subgroup N<50. Children = mix of children and young pple, also N<50.
BLACK 2013 MH Black, Jean M. Lawrence, Catherine Pihoker, Lawrence M. Dolan, Andrea Anderson, Beatriz Rodriguez, Santica M. Marcovina, Elizabeth J.	Mixed population of all ages, with no age subgroup analyses.

Reference	Reason for exclusion
Mayer-Davis, Giuseppina Imperatore, Dana Dabelea, and SEARCH for Diabetes in Youth Study Group. HLA-associated phenotypes in youth with autoimmune diabetes. *Pediatr.Diabetes* 14 (2):121-128, 2013.	
BOROWIEC 2012 M. Borowiec, W. Fendler, P. Dusatkova, K. Antosik, S. Pruhova, O. Cinek, M. Mysliwiec, P. Jarosz-Chobot, M. T. Malecki, and W. Mlynarski. HbA1c-based diabetes diagnosis among patients with glucokinase mutation (GCK-MODY) is affected by a genetic variant of glucose-6-phosphatase (G6PC2). *Diabet.Med.* 29 (11):1465-1469, 2012.	Does no give % of patients with the markers pre-specified in our protocol.
CHAO 2013 C Chao, Gan Huang, Xia Li, Lin Yang, Jian Lin, Ping Jin, Shuo Ming Luo, Yi Yu Zhang, Ling Ling Pan, and Zhi Guang Zhou. Change of glutamic acid decarboxylase antibody and protein tyrosine phosphatase antibody in Chinese patients with acute-onset type 1 diabetes mellitus. *Chin.Med.J.(Engl).* 126 (21):4006-4012, 2013.	Wrong population: mixed population of all ages, with no age sub-group analysis.
EKPEBEGH 2013 C. O. Ekpebegh and B. Longo-Mbenza. Clinical, immunologic and insulin secretory characteristics of young black South African patients with diabetes: Hospital based single centre study. *Diabetes Res.Clin.Pract.* 99 (3):380-384, 2013.	Wrong population: mixed population of all ages, with no age sub-group analysis.
ETO 2012 T. Eto, S. Inoue, and T. Kadowaki. Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: A 4-week, randomized, double-blind, placebo-controlled trial. *Diabestes Obes.Metab.* 14 (11):1040-1046, 2012.	Treatment study.
FERNANDEZ 2013 R Fernandez, Ranjita Misra, Ramaswami Nalini, Christiane S. Hampe, Kerem Ozer, and Ashok Balasubramanyam. Characteristics of patients with ketosis-prone diabetes (KPD) presenting with acute pancreatitis: implications for the natural history and etiology of a KPD subgroup. *Endocr Pract* 19 (2):243-251, 2013.	Unclear if type 1 diabetes or type 2 diabetes – just says ketosis-prone diabetics.
FREDERIKSEN 2013A BN. Frederiksen, Miranda Kroehl, Tasha E. Fingerlin, Randall Wong, Andrea K. Steck, Marian Rewers, and Jill M. Norris. Association between vitamin D metabolism gene polymorphisms and risk of islet autoimmunity and progression to type 1 diabetes: the diabetes autoimmunity study in the young (DAISY). *J.Clin.Endocrinol.Metab.* 98 (11):E1845-E1851, 2013.	Does not answer question: markers as predictors of future development of type 1 diabetes.
HOJSAK 2013 I Hojsak, Noam Zevit, Orith Waisbourd-Zinman, Yoram Rosenbach, Yael Mozer-Glassberg, Shlomit Shalitin, Moshe Phillip, and Raanan Shamir. Concomitant autoantibodies in newly diagnosed diabetic children with transient celiac serology or proven celiac disease. *J.Pediatr.Endocrinol.Metab.* 26 (11-12):1099-1104, 2013.	Wrong population: mixed population of children and young pple, with no age sub-group analysis.
IRGENS 2013	Mixed population of children

Reference	Reason for exclusion
H. U. Irgens, J. Molnes, B. B. Johansson, M. Ringdal, T. Skrivarhaug, D. E. Undlien, O. Sovik, G. Joner, A. Molven, and P. R. Njolstad. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. *Diabetologia* 56 (7):1512-1519, 2013.	and young people; can get data for young people but this is incomplete (some is missing or not available).
JOHNSON 2012 K Johnson, Randall Wong, Katherine J. Barriga, Georgeanna Klingensmith, Anette G. Ziegler, Marian J. Rewers, and Andrea K. Steck. rs11203203 is associated with type 1 diabetes risk in population pre-screened for high-risk HLA-DR,DQ genotypes. *Pediatr.Diabetes* 13 (8):611-615, 2012.	Wrong population: children only.
KARAGUN 2012 B. S. Karagun, F. Temiz, G. Ozer, B. Yuksel, A. K. Topaloglu, N. O. Mungan, M. Mazman, and G. M. Karagun. Chromium levels in healthy and newly diagnosed type 1 diabetic children. *Pediatr Int* 54 (6):780-785, 2012.	Wrong population: children only.
KRAUSE 2012 S Krause, Ruth Chmiel, Ezio Bonifacio, Marlon Scholz, Michael Powell, Jadwiga Furmaniak, Bernard Rees Smith, Anette G. Ziegler, and Peter Achenbach. IA-2 autoantibody affinity in children at risk for type 1 diabetes. *Clin.Immunol.* 145 (3):224-229, 2012.	Wrong population: children only. Risk of future development of type 1 diabetes.
LEE 2013 TH Lee, Ah Reum Kwon, Ye Jin Kim, Hyun Wook Chae, Ho Seong Kim, and Duk Hee Kim. The clinical measures associated with C-peptide decline in patients with type 1 diabetes over 15 years. J Korean Med Sci 28 (9):1340-1344, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
LEMPAINEN 2013 J. Lempainen, T. Harkonen, Ap Laine, M. Knip, J. Ilonen, and Diabetes Register Finnish Pediatric. Associations of polymorphisms in non-HLA loci with autoantibodies at the diagnosis of type 1 diabetes: INS and IKZF4 associate with insulin autoantibodies. *Pediatr.Diabetes* 14 (7):490-496, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
LUDVIGSSON 2013 J Ludvigsson, Annelie Carlsson, Ahmed Deli, Gun Forsander, Sten A. Ivarsson, Ingrid Kockum, Bengt Lindblad, Claude Marcus, Ake Lernmark, and Ulf Samuelsson. Decline of C-peptide during the first year after diagnosis of Type 1 diabetes in children and adolescents. *Diabetes Res.Clin.Pract.* 100 (2):203-209, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
MIAO 2013 D Miao, K. Michelle Guyer, Fran Dong, Ling Jiang, Andrea K. Steck, Marian Rewers, George S. Eisenbarth, and Liping Yu. GAD65 autoantibodies detected by electrochemiluminescence assay identify high risk for type 1 diabetes. *Diabetes* 62 (12):4174-4178, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
MIERSCH 2013 S Miersch, Xiaofang Bian, Garrick Wallstrom, Sahar Sibani, Tanya Logvinenko, Clive H. Wasserfall, Desmond Schatz, Mark Atkinson, Ji Qiu, and	Doesn't give % of pple with Abs or the titre.

Reference	Reason for exclusion
Joshua LaBaer. Serological autoantibody profiling of type 1 diabetes by protein arrays. *J Proteomics* 94:486-496, 2013.	
MORITANI 2013 M. Moritani, I. Yokota, K. Tsubouchi, R. Takaya, K. Takemoto, K. Minamitani, T. Urakami, T. Kawamura, N. Kikuchi, M. Itakura, T. Ogata, S. Sugihara, and S. Amemiya. Identification of INS and KCNJ11 gene mutations in type 1B diabetes in Japanese children with onset of diabetes before 5 yr of age. *Pediatr.Diabetes* 14 (2):112-120, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis. Doesn't give results for our pre-specified markers.
MUGHAL 2013 S. A. Mughal, R. Park, N. Nowak, A. L. Gloyn, F. Karpe, H. Matile, M. T. Malecki, M. I. McCarthy, M. Stoffel, and K. R. Owen. Apolipoprotein M can discriminate HNF1A-MODY from Type 1 diabetes. *Diabet.Med.* 30 (2):246-250, 2013.	Doesn't look at the markers pre-specified in our protocol.
PETRUZELKOVA 2014 L. Petruzelkova, R. Ananieva-Jordanova, J. Vcelakova, Z. Vesely, K. Stechova, J. Lebl, P. Dusatkova, Z. Sumnik, R. Coles, M. Powell, J. Furmaniak, Smith B. Rees, and S. Kolouskova. The dynamic changes of zinc transporter 8 autoantibodies in Czech children from the onset of Type 1 diabetes mellitus. *Diabet.Med.* 31 (2):165-171, 2014.	Wrong population: mix of children and young people, with no age subgroup analysis.
PHAM 2013 MN Pham, Hubert Kolb, Thomas Mandrup-Poulsen, Tadej Battelino, Johnny Ludvigsson, Paolo Pozzilli, Michael Roden, Nanette C. Schloot, and C. P. European. Serum adipokines as biomarkers of beta-cell function in patients with type 1 diabetes: positive association with leptin and resistin and negative association with adiponectin. Diabetes.Metab.Res.Rev. 29 (2):166-170, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
PIHOKER 2013A C Pihoker, Lisa K. Gilliam, Sian Ellard, Dana Dabelea, Cralen Davis,et al and SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J.Clin.Endocrinol.Metab.* 98 (10):4055-4062, 2013.	Wrong population: mix of all ages, with no age subgroup analysis.
REDONDO 2012 MJ. Redondo, Luisa M. Rodriguez, Mirna Escalante, E. O'Brian Smith, Ashok Balasubramanyam, and Morey W. Haymond. Beta cell function and BMI in ethnically diverse children with newly diagnosed autoimmune type 1 diabetes. *Pediatr.Diabetes* 13 (7):564-571, 2012.	Wrong population: mix of children and young people, with no age subgroup analysis.
REDONDO 2013 M. J. Redondo, L. M. Rodriguez, M. Escalante, E. O. Smith, A. Balasubramanyam, and M. W. Haymond. Types of pediatric diabetes mellitus defined by anti-islet autoimmunity and random C-peptide at diagnosis. Pediatr.Diabetes 14 (5):333-340, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
SHERR 2014 JL. Sherr, Tara Ghazi, Anna Wurtz, Linda Rink, and Kevan C. Herold.	Wrong population: mix of all ages, with no age subgroup

Reference	Reason for exclusion
Characterization of residual beta cell function in long-standing type 1 diabetes. *Diabetes.Metab.Res.Rev.* 30 (2):154-162, 2014.	analysis.
SORGJERD 2013 E Pettersen Sorgjerd, Frank Skorpen, Kirsti Kvaloy, Kristian Midthjell, and Valdemar Grill. Prevalence of ZnT8 antibody in relation to phenotype and SLC30A8 polymorphism in adult autoimmune diabetes: results from the HUNT study, Norway. *Autoimmunity* 46 (1):74-79, 2013.	Wrong population: mix of all ages, with no age subgroup analysis.
SOSENKO 2013 JM. Sosenko, Jay S. Skyler, Jerry P. Palmer, Jeffrey P. Krischer, et al Diabetes TrialNet Study Group, and Prevention Trial-Type Diabetes. The prediction of type 1 diabetes by multiple autoantibody levels and their incorporation into an autoantibody risk score in relatives of type 1 diabetic patients. *Diabetes Care* 36 (9):2615-2620, 2013.	Does not answer the question: uses markers as predictors of future development of type 1 diabetes.
XU 2012 P Xu, Craig A. Beam, David Cuthbertson, Jay M. Sosenko, Jay S. Skyler, Jeffrey P. Krischer, and Study Group. Prognostic accuracy of immunologic and metabolic markers for type 1 diabetes in a high-risk population: receiver operating characteristic analysis. *Diabetes Care* 35 (10):1975-1980, 2012.	Does not answer the question: uses markers as predictors of future development of type 1 diabetes.
YU 2013 L Yu, Fran Dong, Dongmei Miao, Alexandra R. Fouts, Janet M. Wenzlau, and Andrea K. Steck. Proinsulin/Insulin autoantibodies measured with electrochemiluminescent assay are the earliest indicator of prediabetic islet autoimmunity. *Diabetes Care* 36 (8):2266-2270, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
CHAI 2014 SY Chai, Xiao Yu Pan, Ke Xiu Song, Yue Ye Huang, Fei Li, Xiao Yun Cheng, and Shen Qu. Differential patterns of insulin secretion and sensitivity in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease versus patients with type 2 diabetes mellitus alone. *Lipids health dis.* 13:7, 2014.	Adults but N<50
DEMIRBILEK 2013 H. Demirbilek, Ozbek M. Nuri, and Baran R. Taner. Incidence of type 1 diabetes mellitus in Turkish children from the Southeastern region of the country: A regional report. *JCRPE J.Clin.Res.Pediatr.Endocrinol.* 5 (2):98-103, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
DONELAN 2013 W Donelan, Hai Wang, Shi Wu Li, David Pittman, Yi Li, Shuhong Han, Yu Sun, Christopher Carter, Mark Atkinson, Westley Reeves, William E. Winter, and Li Jun Yang. Novel detection of pancreatic and duodenal homeobox 1 autoantibodies (PAA) in human sera using luciferase immunoprecipitation systems (LIPS) assay. *Int J Clin Exp Pathol* 6 (6):1202-1210, 2013.	Validation study of new methods for Ab detection.
EKHOLM 2012 E. Ekholm, N. Shaat, and J. J. Holst. Characterization of beta cell and incretin function in patients with MODY1 (HNF4A MODY) and MODY3 (HNF1A MODY) in a Swedish patient collection. Acta Diabetol. 49 (5):349-354, 2012.	Adults but N<50

Reference	Reason for exclusion
EKPEBEGH 2013A C Ekpebegh, Benjamin Longo-Mbenza, and Ernesto Blanco-Blanco. Islet immunity and beta cell reserve of indigenous Black South Africans with ketoacidosis at initial diagnosis of diabetes. *Ethn Dis* 23 (2):196-201, 2013.	Unclear population: just says DKA. Most were later recognised as type 2 diabetes (in the discussion section), but no analysis done by type of diabetes.
HUANG 2012 G Huang, Xuxu Mo, Muwen Li, Yufei Xiang, Xia Li, Shuoming Luo, and Zhiguang Zhou. Autoantibodies to CCL3 are of low sensitivity and specificity for the diagnosis of type 1 diabetes. *Acta Diabetol.* 49 (5):395-399, 2012.	Wrong population: mix of all ages, with no age subgroup analysis.
KAMALALANANI 2013 N. M. Kamal Alanani and A. A. Alsulaimani. Epidemiological pattern of newly diagnosed children with type 1 diabetes mellitus, Taif, Saudi Arabia. *Sci.World J.* 2013, 2013.	Wrong population: children
KIKKAS 2013 I Kikkas, Roberto Mallone, Nadia Tubiana-Rufi, Didier Chevenne, Jean Claude Carel, Christophe Creminon, Herve Volland, Christian Boitard, and Nathalie Morel. A simple and fast non-radioactive bridging immunoassay for insulin autoantibodies. *PloS one* 8 (7):e69021, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
KOLB 2013 H Kolb, Kathrin Luckemeyer, Tim Heise, Christian Herder, Nanette C. Schloot, Wolfgang Koenig, Lutz Heinemann, Stephan Martin, and DIATOR Study Group. The systemic immune network in recent onset type 1 diabetes: central role of interleukin-1 receptor antagonist (DIATOR Trial). *PloS one* 8 (8):e72440, 2013.	Does not give levels or % of pts with markers; just correlations with other markers.
MASALA 2013 S Masala, Maria Antonietta Zedda, Davide Cossu, Carlo Ripoli, Mario Palermo, and Leonardo A. Sechi. Zinc transporter 8 and MAP3865c homologous epitopes are recognized at T1D onset in Sardinian children. *PloS one* 8 (5):e63371, 2013.	Wrong population: children
MUNI 2013 RH. Muni, Radha P. Kohly, Eudocia Q. Lee, JoAnn E. Manson, Richard D. Semba, and Debra A. Schaumberg. Prospective study of inflammatory biomarkers and risk of diabetic retinopathy in the diabetes control and complications trial. *JAMA Ophthalmol* 131 (4):514-521, 2013.	Wrong markers: not those pre-specified in our protocol.
PARKKOLA 2013A A Parkkola, Taina Harkonen, Samppa J. Ryhanen, Jorma Ilonen, Mikael Knip, and Diabetes Register Finnish Pediatric. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. *Diabetes Care* 36 (2):348-354, 2013.	Wrong population: mix of children and young people, with no age subgroup analysis.
RYDEN 2013 A Ryden and Maria Faresjo. Altered immune profile from pre-diabetes to manifestation of type 1 diabetes. Diabetes Res.Clin.Pract. 100 (1):74-84,	Wrong population: mix of children and young people, with no age subgroup

Reference	Reason for exclusion
2013 .	analysis.
SKARSTRAND 2013 H Skarstrand, L. B. Dahlin, A. Lernmark, and F. Vaziri-Sani. Neuropeptide Y autoantibodies in patients with long-term type 1 and type 2 diabetes and neuropathy. *J.Diabetes Complications* 27 (6):609-617, 2013.	Wrong population: mix of all ages, with no age subgroup analysis.
VARADARAJAN 2013 P Varadarajan, Thangavelu Sangaralingam, Senthil Senniappan, Suresh Jahnavi, Venkatesan Radha, and Viswanathan Mohan. Clinical profile and outcome of infantile onset diabetes mellitus in southern India. *Indian Pediatr* 50 (8):759-763, 2013.	Wrong population: children
VCELAKOVA 2013 J Vcelakova, Radek Blatny, Zbynek Halbhuber, Michal Kolar, Ales Neuwirth, et al. The effect of diabetes-associated autoantigens on cell processes in human PBMCs and their relevance to autoimmune diabetes development. *J Diabetes Res* 2013:589451, 2013.	Wrong population: mix of all ages, with no age subgroup analysis.
WARNCKE 2013 K Warncke, M Krasmann, R Puff, D Dunstheimer, AG Ziegler, and A Beyerlein. Does diabetes appear in distinct phenotypes in young people? Results of the diabetes mellitus incidence Cohort Registry (DiMelli). *PloS one* 8 (9):e74339, 2013.	Wrong population: mix of all ages, with no age subgroup analysis.
WILLIAMS 2012 AJ. K. Williams, SL. Thrower, IM. Sequeiros, A Ward, AS. Bickerton, JM. Triay, MP. Callaway, and CM. Dayan. Pancreatic volume is reduced in adult patients with recently diagnosed type 1 diabetes. *J.Clin.Endocrinol.Metab.* 97 (11):E2109-E2113, 2012.	Adults, but N<50.
ZAHARAN 2012 A M Zahran, KI Elsayh, and K A Metwalley. Regulatory T cells in children with recently diagnosed type 1 diabetes. *Indian J Endocrinol Metab* 16 (6):952-957, 2012.	Wrong population: children
ZIEGLER 2013A AG. Ziegler, M Rewers, O Simell, T Simell, J Lempainen, A Steck, C Winkler, J Ilonen, R Veijola, M Knip, E Bonifacio, and GS. Eisenbarth. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA* 309 (23):2473-2479, 2013.	Does not answer the question: uses markers as predictors of future development of type 1 diabetes.
HARTEMANN 2013 Hartemann A, Bensimon G, Payan CA, Jacqueminet S, Bourron O, Nicolas N et al. Low-dose interleukin 2 in patients with type 1 diabetes: A phase 1/2 randomised, double-blind, placebo-controlled trial. Lancet Diabetes and Endocrinology. 2013; 1(4):295-305	Treatment study. Article currently unavailable.
PAPADIMITRIOU 2013 DT. Papadimitriou, C Marakaki, A Fretzayas, P Nicolaidou, and A Papadimitriou. Negativation of type 1 diabetes-associated autoantibodies to	Article currently unavailable.

Reference	Reason for exclusion
glutamic acid decarboxylase and insulin in children treated with oral calcitriol. *J Diabetes* 5 (3):344-348, 2013.	
AITKEN 2014 R. J. Aitken, I. V. Wilson, A. E. Long, A. J. K. Williams, T. J. McDonald, K. M. Gillespie, F. S. Wong, A. T. Hattersley, and P. J. Bingley. Residual beta cell function in long-standing childhood onset Type 1 diabetes. *Diabet Med* 31:19-20, 2014.	Conference abstract
AL-FARWI 2014 A. Al-Farwi. The prevalence, autoimmune and genetic markers of latent autoimmune diabetes of adults in the coastal area/Syria. *Diabetes Technol.Ther.* 16:A135, 2014.	Conference abstract
ANDERSSON 2014 C Andersson, M Kolmodin, S A Ivarsson, A Carlsson, G Forsander, B Lindblad, J Ludvigsson, I Kockum, C Marcus et al and Better Diabetes Diagnosis Study Group. Islet cell antibodies (ICA) identify autoimmunity in children with new onset diabetes mellitus negative for other islet cell antibodies. *Pediatr Diabetes* 15 (5):336-344, 2014	Unable to acquire article. Also in children.
AXELSSON 2012 S. Axelsson, M. Hjorth, J. Ludvigsson, and R. Casas. Decreased GAD(65)-specific Th1/Tc1 phenotype in children with Type 1 diabetes treated with GAD-alum. *Diabet Med* 29 (10):1272-1278, 2012.	Does not give the results for our pre-specifed markers of interest.
BOSSOWSKI 2013 A. Bossowski, J. Furmaniak, J. Michalak, T. Diana, B. Glowin'ska-Olszewska, and G. Kahaly. Assessment of the occurance of the autoantibodies in children with diabetes type 1. *Pediatr Diabetes* 14:125, 2013.	Conference abstract
BRAHAM 2014 R. Braham, A. A. Zaid, R. Ahmed, M. Zitouni, S. Sobki, and F. A. Sabaan. Double diabetes in Saudi Arabia: A new entity or an underestimated condition? *Diabetes* 63:A402, 2014.	Conference abstract
BRAVIS 2014 V. Bravis, A. Kaur, H. Walkey, I. Godsland, C. Dayan, M. Peakman, P. Bingley, and D. G. Johnston. An incident and high-risk type 1 diabetes cohort-after diagnosis diabetes research support system-2 (address-2): Key initial findings. *Diabetes* 63:A645, 2014.	Conference abstract
BUCKINGHAM 2014 B. A. Buckingham, P. Cheng, R. W. Beck, C. Kollman, K. Ruedy, S. A. Weinzimer, R. Slover, A. A. Bremer, W. V. Tamborlane, and J. Fuqua. Relationship of glycemic control and c-peptide levels 2 years following diagnosis of T1D. *Diabetes* 63:A392, 2014.	Conference abstract
CALLIARI 2014 L. E. Calliari, B. L. Barbosa, D. C. F. Lago, R. M. Noronha, and A. F. Reis. Maturity-onset diabetes of the young (MODY) type 2 in infancy and	Conference abstract

Reference	Reason for exclusion
adolescence: Description of three families. *Pediatr Diabetes* 14:133, 2013.	
CASTLEDEN 2014 H. A. Castleden, A. E. Long, I. V. Wilson, R. J. Aitken, A. J. Williams, P. J. Bingley, and K. M. Gillespie. The characteristics of slow progression to Type 1 diabetes. *Diabet Med* 31:19, 2014.	Conference abstract
CERQUEIRO 2013 BM. Cerqueiro, L. Grahnquist, E. Ortqvist, A. Carlsson, and S. Ivarsson. Transglutaminas antibodies in Swedish children with type 1 diabetes in relation to HLA types and islet autoantibodies. *Pediatr Diabetes* 14:128-129, 2013.	Conference abstract
CHAMBERS 2014 C. M. Chambers, A. R. Fouts, R. M. Sippl, K. Colclough, Z. X. Wang, Batish S. Dev, M. Jaremko, S. Ellard, A. T. Hattersley, G. J. Klingensmith, and A. K. Steck. Characteristics of maturity onset diabetes of the young in a large diabetes center. *Diabetes* 63:A363, 2014.	Conference abstract
DANIELSON 2014 K. K. Danielson, R. S. Monson, and T. J. Lecaire. Lower residual c-peptide at type 1 diabetes diagnosis and poor 10-year glycemic control independently predict higher pro-inflam matory tumor necrosis factor-alpha at 13-18 years diabetes duration. *Diabetes* 63:A409, 2014.	Conference abstract
DIMEGLIO 2014 L. A. Dimeglio, P. Cheng, R. W. Beck, C. Kollman, K. Ruedy, B. A. Buckingham, S. A. Weinzimer, R. Slover, A. A. Bremer, and T. Aye. Early predictors of stimulated C-peptide in persons with type 1 diabetes (T1D). *Diabetes* 63:A392, 2014.	Conference abstract
ELDING 2014 LH. Elding, K. Vehik, P. Gesualdo, B. Akolkar, W. Hagopian, J. Krischer, A. Lernmark, M. Rewers, O. Simell, J.-X. She, A. Ziegler, and M. J. Haller. Children followed in the TEDDY study are diagnosed with type 1 diabetes at an early stage of disease. *Pediatr Diabetes* 15 (2):118-126, 2014.	Does not answer question: presence of Abs BEFORE diagnosis.
FAN 2013 H Fan, QingRong Pan, Pengrui Zhang, Jia Liu, Yuan Xu, and Xinchun Yang. Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. *Med Sci Monit* 19:787-793, 2013.	Already found this study in first set of reruns. Has been included in review.
FERNANDEZ 2013 LA. Fernandez, Moreira Garcia, V, Gonzalez B. Laborda, Corona L. Marcos, N. Beridze, and Rodriguez E. Fernandez. Stability of C-peptide in blood specimens after delayed processing. *Biochim.Clin.* 37:S331, 2013.	Conference abstract
GARBER 2014 E. Graber, M. Regelmann, E. Wallach, L. Waldman, M. Goldis, M. Klein, D. Chia, and R. Rapaport. C-peptide is detected in 40% of youth with long-standing type 1 diabetes: A pilot study. *Diabetes* 63:A320, 2014.	Conference abstract

Reference	Reason for exclusion
HABU 2013 M. Habu, R. Kuwabara, M. Okuno, J. Suzuki, T. Urakami, and S. Takahashi. Prevalences of antibodies to IA-2 and GAD at the time of diagnosis in children with type1 diabetes. *Pediatr Diabetes* 14:123, 2013.	Conference abstract
JOHNSON 2014 C. C. Johnson, K. A. Mclaughlin, D. Morgan, R. G. Feltbower, and M. R. Christie. Fine mapping of epitopes for antibodies to the juxtamembrane domain of IA-2 in type 1 diabetes. *Diabetes* 63:A430, 2014.	Conference abstract
JUHL 2014 C. B. Juhl, U. Bradley, J. J. Holst, R. D. Leslie, K. B. Yderstraede, and S. Hunter. Similar weight-adjusted insulin secretion and insulin sensitivity in short-duration late autoimmune diabetes of adulthood (LADA) and Type 2 diabetes: Action LADA 8. *Diabet Med* 31 (8):941-945, 2014.	N<50
JUNG 2014 ES Jung, Dong Kyun Han, Eun Mi Yang, Min Sun Kim, Dae Yeol Lee, and Chan Jong Kim. Thyroid autoimmunity in children and adolescents with newly diagnosed type 1 diabetes mellitus. *Ann.pediatr.endocrinol.metab.* 19 (2):76-79, 2014.	Wrong population: children.
KAMALALANANI 2013 N Mohamed Kamal Alanani and AA Alsulaimani. Epidemiological pattern of newly diagnosed children with type 1 diabetes mellitus, Taif, Saudi Arabia. *ScientificWorldJournal* 2013:421569, 2013.	Already found this study in first set of reruns. Has been excluded from review as children population.
KANTHIMATHI 2014 S. Kanthimathi, S. Jahnavi, K. Balamurugan, H. Ranjani, J. Sonya, S. Goswami, S. Chowdhury, V. Mohan, and V. Radha. Glucokinase gene mutations (MODY 2) in Asian Indians. *Diabetes Technol.Ther.* 16 (3):180-185, 2014.	Wrong population: not diabetic.
KAWASAKI 2014 E. Kawasaki, T. Maruyama, A. Imagawa, T. Awata, H. Ikegami, Y. Uchigata, H. Osawa, Y. Kawabata, T. Kobayashi, A. Shimada, I. Shimizu, K. Takahashi, M. Nagata, H. Makino, and T. Hanafusa. Diagnostic criteria for acute-onset type 1 diabetes mellitus (2012): Report of the committee of Japan diabetes society on the research of fulminant and acute-onset type 1 diabetes mellitus. *J.diabetes investig.* 5 (1):115-118, 2014.	Wrong population: fulminant and acute type 1 diabetes.
KAWASAKI 2014 E Kawasaki, Megumi Tanaka, Masaki Miwa, Norio Abiru, and Atsushi Kawakami. Novel enzyme-linked immunosorbent assay for bivalent ZnT8 autoantibodies. *Acta Diabetol* 51 (3):429-434, 2014.	Wrong population: all ages mixed.
KHODAGHALIAN 2014 B. Khodaghalian, A. U. Nayak, G. I. Varughese, and P. Raffeeq. Association of anti-GAD antibodies at diagnosis with glycaemia at 6 months in children with type 1 diabetes. *Diabetes* 63:A627, 2014.	Conference abstract

Reference	Reason for exclusion
KIKKAS 2014 I Kikkas, Roberto Mallone, Etienne Larger, Herve Volland, and Nathalie Morel. A Rapid Lateral Flow Immunoassay for the Detection of Tyrosine Phosphatase-Like Protein IA-2 Autoantibodies in Human Serum. *PloS one* 9 (7):e103088, 2014.	Wrong sample size. N<50
KONG 2013 YH Kong, Min Sun Kim, and Dae Yeol Lee. Comparison of the prevalence of islet autoantibodies according to age and disease duration in patients with type 1 diabetes mellitus. *Ann.pediatr.endocrinol.metab.* 18 (2):65-70, 2013.	Wrong sample size: adult subgroup is N<50; adult and young pple mixed subgroup isalso N<50.
KOO 2014 B Kyung Koo, Sehyun Chae, Kristine M. Kim, Min Jueng Kang, Eunhee G. Kim, Soo Heon Kwak, Hye Seung Jung, et al. Identification of novel autoantibodies in type 1 diabetic patients using a high-density protein microarray. *Diabetes* 63 (9):3022-3032, 2014.	Unable to obtain article.
KOSKINEN 2013 M. K. Koskinen, R. Hermann, J. Matomaki, J. Mykkanen, M. Vaha-Makila, T. Simell, S. Simell, M. Makinen, V. Simell, M. Saarinen, J. Ilonen, M. Knip, and O. Simell. Insulin resistance, beta cell function and the effect of non-HLA genetic variants in Finnish DIPP study children with HLA-conferred risk for type 1 diabetes. *Diabetologia* 56:S229, 2013.	Conference abstract
LEE 2014A JE Lee, Ji Woo Lee, Tatsuyoshi Fujii, Noriyoshi Fujii, and Jong Weon Choi. The ratio of estimated average glucose to fasting plasma glucose level is superior to glycated albumin, hemoglobin A1c, fructosamine, and GA/A1c ratio for assessing beta-cell function in childhood diabetes. *Biomed Res Int* 2014:370790, 2014.	Wrong population: children and young people
LEMPAINEN 2013 J. Lempainen, A.-P. Laine, A. Hammais, R. Veijola, O. Simell, M. Knip, and J. Ilonen. PTPN2 rs45450798 polymorphism is associated with accelerated progression of beta cell autoimmunity to clinical type 1 diabetes. *Diabetologia* 56:S18, 2013.	Conference abstract
LERNMARK 2013 A. Lernmark. The environmental determinants of diabetes in the young (TEDDY) and prospects of prevention. *Pediatr Diabetes* 14:1-2, 2013.	Conference abstract
LILLEKER 2013 J. Lilleker, V. Biswas, and R. Mohanraj. Relevance of gad antibodies in adults with epilepsy: Experience in a tertiary clinic. *J.Neurol.Neurosurg.Psychiatry* 84 (11), 2013.	Conference abstract
LUDVIGSSON 2013 J. Ludvigsson, D. Krisky, R. Casas, T. Battelino, L. Castano, J. Greening, O. Kordonouri, T. Otonkoski, P. Pozzilli, J. J. Robert, H. J. Veeze, and J. Palmer. GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus. *Diabetes Technol.Ther.* 15 (SUPPL.1):S92-S93, 2013.	Conference abstract

Reference	Reason for exclusion
MADDALONI 2014 E. Maddaloni, N. Lessan, A. A. Tikriti, P. Pozzilli, and M. T. Barakat. Prevalence and features of adult-onset autoimmune diabetes in the United Arab Emirates (UAE). *Diabetes* 63:A399, 2014.	Conference abstract
MAJIDI 2014 S. Majidi, A. R. Fouts, T. Armstrong, R. M. Sippl, K. Colclough, Z. Wang, D. S. Batish, M. Jaremko, S. Ellard, A. T. Hattersley, G. J. Klingensmith, and A. K. Steck. Hla typing and C-peptide measurement to target mody genetic testing in antibody-negative diabetes. *Diabetes* 63:A354, 2014.	Conference abstract
MASALA 2014 S Masala, Davide Cossu, Simona Piccinini, Novella Rapini, Arianna Massimi, Ottavia Porzio, Silvia Pietrosanti, Roberta Lidano, Maria Luisa Manca Bitti, and Leonardo Antonio Sechi. Recognition of zinc transporter 8 and MAP3865c homologous epitopes by new-onset type 1 diabetes children from continental Italy. *Acta Diabetol* 51 (4):577-585, 2014.	Wrong population: children and young people
MATTER 2013 R. Matter, A. Adly, M. M. Abd El Aziz, and D. Toima. Serum CXC chemokine ligand 10 (CXCL10) in type 1 diabetic children, adolescents, and subjects at high risk of type 1 diabetes. *Pediatr Diabetes* 14:44, 2013.	Conference abstract
MAURIZI 2011 A. Maurizi, R. Strollo, P. Pozzilli, and N. Napoli. Osteocalcin and residual beta-cell function in type 1 diabetes. *J.Bone Miner.Res.* 26, 2011.	Conference abstract
MAXANDERSEN 2014 M L Max Andersen, Lotte B. Nielsen, Jannet Svensson, Sven Porksen, Philip Hougaard, Craig Beam, Carla Greenbaum, Dorothy Becker, Jacob S. Petersen, Lars Hansen, and Henrik B. Mortensen. Disease progression among 446 children with newly diagnosed type 1 diabetes located in Scandinavia, Europe, and North America during the last 27yr. *Pediatr Diabetes* 15 (5):345-354, 2014.	Wrong population: children and young people
MESSAAOUI 2013 A. Messaaoui, S. Tenoutasse, C. Melot, and H. Dorchy. Inverse relationship between increased glomerular filtration rate and C-peptide level at diagnosis of type 1 diabetes in children and adolescents. *Pediatr Diabetes* 14:21-22, 2013.	Conference abstract
MUL 2013 D. Mul, T. C. Sas, J. J. Schermer-Rotte, and H. J. Veeze. Completeness of immunological testing at diagnosis of diabetes mellitus in the Paediatric Diabetes Registry in the Netherlands (PDR.NL). *Pediatr Diabetes* 14:123-124, 2013.	Conference abstract
NUGENT 2012 K. Nugent, C. M. McDonnell, and N. P. Murphy. Autoantibodies in type 1 diabetes: Are we different? *Ir.J.Med.Sci.* 181:S105, 2012.	Conference abstract

Reference	Reason for exclusion
ORAM 2014 R. A. Oram, T. J. McDonald, B. M. Shields, E. R. Pearson, and A. T. Hattersley. A large, population-based study demonstrates that most people with long duration Type 1 diabetes are insulin microsecretors and produce their own endogenous insulin. *Diabet Med* 31:10, 2014.	Conference abstract
PADOA 2013 C. J. Padoa, P. Rheeder, and N. J. Crowther. Phenotypic and genotypic characterisation of type 1 diabetes mellitus in black South African patients. *J.Endocrinol.Metab.Diabetes S.Afr.* 18 (1):37, 2013.	Conference abstract
PEDERSEN 2014 M L Pedersen, Peter Bjerregaard, and Marit Eika Jorgensen. GAD65 antibodies among Greenland Inuit and its relation to glucose intolerance. *Acta Diabetol* 51 (4):641-646, 2014.	Wrong population: not generalizable/applicable to UK population.
PIEKARSKI 2014 R. Piekarski, J. Tabarkiewicz, A. Bojarska-Junak, and L. Szewczyk. Dynamic changes of the TH17 cell population in children with new-onset type 1 diabetes. *Diabetes* 63:A625-A626, 2014.	Conference abstract
PIEKARSKI 2013 R. Piekarski, B. Wilczyn'ska, A. Bojarska-Junak, and J. Tabarkiewicz. Th17 cells in children with new onset type 1 diabetes-preliminary report. *Pediatr Diabetes* 14:123, 2013.	Conference abstract
POWELL 2014 W. E. Powell, C. N. Janicki, A. Howell, A. Bishop, C. M. Dayan, and F. S. Wong. Developing an assay to detect B-cell responses to autoantigens GAD and IA-2 in Type 1 diabetes. *Diabet Med* 31:47, 2014.	Conference abstract
PRODAM 2014 F Prodam, Francesco Cadario, Simonetta Bellone, Letizia Trovato, Stefania Moia, Erica Pozzi, Silvia Savastio, and Gianni Bona. Obestatin levels are associated with C-peptide and antiinsulin antibodies at the onset, whereas unacylated and acylated ghrelin levels are not predictive of long-term metabolic control in children with type 1 diabetes. *J Clin Endocrinol Metab* 99 (4):E599-E607, 2014.	Unable to obtain article.
REDONDO 2014 M. J. Redondo, N. Bansal, L. M. Rodriguez, J. A. Kushner, C. S. Hampe, and A. Balasubramanyam. Dpd epitope-specific GAD65 autoantibody is associated with older age of onset and obesity in pediatric type 1 diabetes. *Diabetes* 63:A8, 2014.	Conference abstract
REWERS 2013 M. Rewers, K. Waugh, K. Barriga, J. Norris, and J. Snell-Bergeon. Lower physical activity in children with persistent islet autoantibodies than in matched controls. *Diabetologia* 56:S132-S133, 2013.	Conference abstract

Reference	Reason for exclusion
SERBAN 2013 V. Serban, F. Fiera, and B. Timar. Basal C-peptide behavior and its clinical significance in Romanian children with type 1 diabetes. *Pediatr Diabetes* 14:80, 2013.	Conference abstract
SHIELDS 2014 B. M. Shields, M. Hudson, M. Shepherd, R. Oram, T. J. McDonald, S. Ellard, E. R. Pearson, and A. T. Hattersley. Comparison of screening using clinical criteria and biomarkers to identify maturity-onset diabetes of the young (MODY) in a community based setting. *Diabet Med* 31:20, 2014.	Conference abstract
SHIVAPRASAD 2014 C. Shivaprasad, Rajneesh Mittal, Mala Dharmalingam, and Prasanna K. Kumar. Zinc transporter-8 autoantibodies can replace IA-2 autoantibodies as a serological marker for juvenile onset type 1 diabetes in India. *Indian J Endocrinol Metab* 18 (3):345-349, 2014.	Wrong population: young people. FOR CHILDREN/YOUNG PPLE GUIDELINE
SIJANDER 2013 H. Siljander, A. Peet, V. Tillmann, T. Harkonen, O. Niemela, J. Ilonen, Hertzen L. Von, T. Haahtela, Mutius E. Von, and M. Knip. Relation between beta cell autoimmunity and levels of allergen-specific IgEs in young Finnish and Estonian children. *Diabetologia* 56:S18, 2013.	Conference abstract
SKARSTRAND 2013 H. Skarstrand, F. Vaziri-Sani, C. Andersson, H. Elding-Larsson, S. Ivarsson, and A. Lernmark. NPY minor autoantibodies in newly diagnosed type 1 diabetes patients. *Diabetologia* 56:S19, 2013.	Conference abstract
STIDSEN 2014 J. V. Stidsen, R. W. Thomsen, J. S. Nielsen, J. Rungby, S. P. Ulrichsen, K. Berensci, S. Friborg, I. Brandslund, A. A. Nielsen, J. S. Christiansen, H. Sorensen, A. A. Vaag, T. B. Olesen, M. H. Olsen, J. E. Henriksen, and H. Beck-Nielsen. Pathophysiological phenotypes of clinically diagnosed type 2 diabetes. *Diabetes* 63:A354-A355, 2014.	Conference abstract
SUNNI 2013 M. S. Sunni, M. Farah, J. Smith, A. Dhunkal, M. D. Bellin, B. M. Nathan, P. A. Gottlieb, L. Yu, S. Babu, T. Armstrong, and A. Moran. HLA alleles and diabetes autoantibodies in a group of Somali children with type 1 diabetes in the Twin Cities, Minnesota: A pilot study. *Pediatr Diabetes* 14:129, 2013.	Conference abstract
TAKEZAWA 2009 J Takezawa, Kouichi Yamada, Akemi Morita, Naomi Aiba, and Shaw Watanabe. Preproghrelin gene polymorphisms in obese Japanese: Association with diabetes mellitus in men and with metabolic syndrome parameters in women. *Obes Res Clin Pract* 3 (4):179-191, 2009.	Wrong population: mixed diabetes subgroup.
URBANOVA 2014 J. Urbanova, B. Rypackova, Z. Prochazkova, P. Kucera, M. Cerna, M. Andel, and P. Heneberg. Positivity for islet cell autoantibodies in patients with monogenic diabetes is associated with later diabetes onset and higher	Wrong population: mixed agaes, and N<50.

Reference	Reason for exclusion
HbA1c level. *Diabet Med* 31 (4):466-471, 2014.	
WALLACE 2014 I. Wallace, S. Chan, M. Naidu, B. Secret, G. Braatvedt, and M. Khanolkar. A 6 year retrospective observational study: Autoantibodies to glutamic acid decarboxylase (GAD) and insulinoma antigen 2 (IA-2) in patients newly diagnosed with adult diabetes presenting with diabetic ketoacidosis. *Diabet Med* 31:181, 2014.	Conference abstract
WARNCKE 2013 K Warncke, Miriam Krasmann, Ramona Puff, Desiree Dunstheimer, Anette Gabriele Ziegler, and Andreas Beyerlein. Does diabetes appear in distinct phenotypes in young people? Results of the diabetes mellitus incidence Cohort Registry (DiMelli). *PloS one* 8 (9):e74339, 2013.	Already found article in first reruns. Was excluded from review as wrong population – mixed ages.
WATKINS 2013 R. A. Watkins, C. Evans-Molina, J. Terrell, K. Day, L. Guindon, R. G. Mirmira, J. S. Blum, and L. A. Di Meglio. Persistence of beta cell stress in the initial period following diagnosis of T1D in children. *Pediatr Diabetes* 14:68, 2013.	Conference abstract
WILHELM 2013 K. Wilhelm, K. Tornow, V. Lampasona, U. Walschus, I. Rjasanowski, W. Kerner, and M. Schlosser. Prognostic and diagnostic relevance of ZnT8 antibodies in autoimmune diabetes. *Diabetologia* 56:S133, 2013.	Conference abstract
XU 2014 P. Xu, X. Qian, D. A. Schatz, D. Cuthbertson, and J. P. Krischer. Distribution of C-peptide and its determinants in North American children at risk for type 1 diabetes. *Diabetes care* 37 (7):1959-1965, 2014.	Wrong population: not diabetes, only those at risk for diabetes.
YILMAZ 2013 AS. Yilmaz, Z. Aycan, S. Cetinkaya, V. N. Bas, A. Onder, H. N. Peltek Kendirci, and S. Ceylaner. Screening for mutations in children with a clinical diagnosis of maturity onset diabetes of youth (MODY). *Pediatr Diabetes* 14:132, 2013.	Conference abstract
ZAGO 2014 S. Zago, M. Fabris, M. Liguori, M. Trevisan, M. Zanatta, A. Comici, G. Zanette, E. Tonutti, and F. Curcio. Improving the diagnostic approach to type I diabetes: The introduction of anti-zinc transporter protein autoantibodies (ZnT8A). *FASEB J.* 28 (1 SUPPL. 1), 2014.	Conference abstract
ZUBKIEWICZ 2013 A. Zubkiewicz-Kucharska, A. Noczyn'ska, and L. Usnarska-Zubkiewicz. Prognostic significance of T lymphocytes in type 1 diabetes in children. *Pediatr Diabetes* 14:124, 2013.	Conference abstract
Studies in all ages, with no adult or young people subgroup analysis	
TOBON 2006 G. J. Tobon, A. Arango, V. Abad, J. Garcia, H. Cuervo, A. Velasquez, I. D. Angel, P. Vega, A. Abad, and J. M. Anaya. Clinical and immunological characteristics of type 1 diabetes mellitus in a northwestern Colombian	Mixed population: all ages with no adult or young people subgroup analysis

Reference	Reason for exclusion
population. *Diabetes Res.Clin.Pract.* 72 (2):170-175, 2006.	
KOGA 2010 M. Koga, J. Murai, H. Saito, S. Kasayama, T. Kobayashi, A. Imagawa, and T. Hanafusa. Correlation of glycated albumin but not hemoglobin A1c with endogenous insulin secretion in fulminant type 1 diabetes mellitus. *J.Diabetes Invest.* 1 (6):279-282, 2010.	Mixed population: all ages with no adult ort young people subgroup analysis. Also wrong type of diabetes: fulminant type 1 diabetes.
TULLOCH 2010 M. K. Tulloch-Reid, M. S. Boyne, M. F. Smikle, E. G. Choo-Kang, R. H. Parkes, R. A. Wright-Pascoe, E. N. Barton, R. J. Wilks, and D. E. Williams. Clinical and laboratory features of youth onset type 2 diabetes in Jamaica. *West Indian Med.J.* 59 (2):131-138, 2010.	Mixed population: all ages with no adult or young people subgroup analysis
SIAFARIKAS 2012 A Siafarikas, RJ. Johnston, MK. Bulsara, P O'Leary, TW. Jones, and EA. Davis. Early loss of the glucagon response to hypoglycemia in adolescents with type 1 diabetes. *Diabetes Care* 35 (8):1757-1762, 2012.	Mixed population: all ages with no adult or young people subgroup analysis
PAN 2004 C. Y. Pan, W. Y. So, B. A. K. Khalid, V. Mohan, A. C. Thai, P. Zimmet, C. S. Cockram, L. N. Jorgensen, J. P. Yeo, and ASDIAB Study Group. Metabolic, immunological and clinical characteristics in newly diagnosed Asian diabetes patients aged 12-40 years. *Diabet.Med.* 21 (9):1007-1013, 2004.	Mixed population: all ages with no adult or young people subgroup analysis
TODD 2004 A. L. Todd, W. Y. Ng, K. F. Lui, and A. C. Thai. Low prevalence of autoimmune diabetes markers in a mixed ethnic population of Singaporean diabetics. *Intern.Med.J.* 34 (1-2):24-30, 2004.	Mixed population: all ages with no adult or young people subgroup analysis
RODACKI 2005 M Rodacki, L Zajdenverg, RP Tortora, FA Reis, MS. Albernaz, MRB Goncalves, A Milech, and JEP de Oliveira. Characteristics of childhood and adult-onset type 1 diabetes in a multi-ethnic population. *Diabetes Res.Clin.Pract.* 69 (1):22-28, 2005.	Mixed population: all ages with no adult or young people subgroup analysis
Studies in children (age <11 years) and young people (age 11-17 years)	
SZYPOWSKA 2011 A Szypowska and A Skorka. The risk factors of ketoacidosis in children with newly diagnosed type 1 diabetes mellitus. *Pediatr Diabetes* 12 (4 Pt 1):302-306, 2011.	Wrong population: children and young people
HAMEED 2011 S. Hameed, S. Ellard, H. J. Woodhead, K. A. Neville, J. L. Walker, M. E. Craig, T. Armstrong, L. Yu, G. S. Eisenbarth, A. T. Hattersley, and C. F. Verge. Persistently autoantibody negative (PAN) type 1 diabetes mellitus in children. *Pediatr Diabetes* 12 (3 PART 1):142-149, 2011.	Wrong population: children and young people
LIPTON 2011 RB. Lipton, ML. Drum, KK. Danielson, S Aw Greeley, GI. Bell, and WA. Hagopian. Onset features and subsequent clinical evolution of childhood	Wrong population: children and young people

Reference	Reason for exclusion
diabetes over several years. *Pediatr Diabetes* 12 (4 Pt 1):326-334, 2011.	
XIN 2010 Y Xin, M Yang, X Juan Chen, YJ Tong, and LH Zhang. Clinical features at the onset of childhood type 1 diabetes mellitus in Shenyang, China. *J.Paediatr.Child Health* 46 (4):171-175, 2010.	Wrong population: children and young people
MORTENSEN 2009 HB. Mortensen, P Hougaard, P Swift, L Hansen, RW. Holl, H Hoey, H Bjoerndalen, C de Beaufort, F Chiarelli, T Danne, EJ. Schoenle, J Aman, and Hvidoere Study Group on Childhood Diabetes. New definition for the partial remission period in children and adolescents with type 1 diabetes. *Diabetes Care* 32 (8):1384-1390, 2009.	
REINEHR 2006 T. Reinehr, E. Schober, S. Wiegand, A. Thon, R. Holl, and DPV-Wiss Study Group. Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification? *Arch.Dis.Child.* 91 (6):473-477, 2006.	
AMUTHA 2012 A. Amutha, M. Datta, R. Unnikrishnan, R. M. Anjana, and V. Mohan. Clinical profile and complications of childhood- and adolescent-onset type 2 diabetes seen at a diabetes center in south India. *Diabetes Technol Ther* 14 (6):497-504, 2012.	
LEVITT 2011 LE. Levitt Katz, SN Magge, ML. Hernandez, KM. Murphy, HM. McKnight, and T Lipman. Glycemic control in youth with type 2 diabetes declines as early as two years after diagnosis. *J.Pediatr.* 158 (1):106-111, 2011.	
MATSUI 2005 J Matsui, N Tamasawa, J Tanabe, N Kasai, H Murakami, K Matsuki, and T Suda. Clinical characteristics of Japanese youth-onset type 2 diabetes with ketonuria. *Diabetes Res.Clin.Pract.* 70 (3):235-238, 2005.	
BRORSSON 2011 C Brorsson, F Vaziri-Sani, R Bergholdt, S Eising, A Nilsson, J Svensson, A Lernmark, F Pociot, and Danish Study Group of Childhood Diabetes. Correlations between islet autoantibody specificity and the SLC30A8 genotype with HLA-DQB1 and metabolic control in new onset type 1 diabetes. *Autoimmunity* 44 (2):107-114, 2011.	
MANAN 2012 H Manan, Al M Angham, and A Sitelbanat. Genetic and diabetic auto-antibody markers in Saudi children with type 1 diabetes. *Hum.Immunol.* 71 (12):1238-1242, 2010.	
ABDELBAKY 2006 A. M. N. E. Abd El Baky, S. M. Abd El Dayem, H. A. Atwa, and H. Rasmy. Assessment of interleukin 18 in children with type 1 diabetes and their relatives: Its relation to autoantibodies. *J.Med.Sci.(Pakistan)* 6 (4):603-608,	

Reference	Reason for exclusion
2006.	
RONKAINEN 2004 M. S. Ronkainen, K. Savola, and M. Knip. Antibodies to GAD65 epitopes at diagnosis and over the first 10 years of clinical type 1 diabetes mellitus. *Scand.J.Immunol.* 59 (3):334-340, 2004.	
ANDERSSON 2011 C. Andersson, K. Larsson, F. Vaziri-Sani, K. Lynch, A. Carlsson, E. Cedervall, B. Jonsson, J. Neiderud, M. Mansson, A. Nilsson, A. Lernmark, H. Elding Larsson, and S. A. Ivarsson. The three ZNT8 autoantibody variants together improve the diagnostic sensitivity of childhood and adolescent type 1 diabetes. *Autoimmunity* 44 (5):394-405, 2011.	
BROOKS 2004 B. M. Brooks-Worrell, C. J. Greenbaum, J. P. Palmer, and C. Pihoker. Autoimmunity to Islet Proteins in Children Diagnosed with New-Onset Diabetes. *J.Clin.Endocrinol.Metab.* 89 (5):2222-2227, 2004.	
KARAGUZEL 2008 G Karaguzel, S Simsek, O Deger, and A Okten. Screening of diabetes, thyroid, and celiac diseases-related autoantibodies in a sample of Turkish children with type 1 diabetes and their siblings. *Diabetes Res.Clin.Pract.* 80 (2):238-243, 2008.	
KAAS 2012 A. Kaas, C. Pfleger, A. V. Kharagjitsingh, N. C. Schloot, L. Hansen, K. Buschard, B. P. C. Koeleman, B. O. Roep, H. B. Mortensen, B. Z. Alizadeh, and Hvidoere Study Group on Childhood Diabetes. Association between age, IL-10, IFNgamma, stimulated C-peptide and disease progression in children with newly diagnosed Type 1 diabetes. *Diabet.Med.* 29 (6):734-741, 2012.	
LOMBARDO 2002 F. Lombardo, M. Valenzise, M. Wasniewska, M. F. Messina, C. Ruggeri, T. Arrigo, and F. De Luca. Two-year prospective evaluation of the factors affecting honeymoon frequency and duration in children with insulin dependent diabetes mellitus: the key-role of age at diagnosis. *Diabetes Nutr Metab* 15 (4):246-251, 2002.	
SALARDI 2003 S. Salardi, S. Zucchini, A. Cicognani, E. Corbelli, R. Santoni, L. Ragni, D. Elleri, and E. Cacciari. The severity of clinical presentation of type 1 diabetes in children does not significantly influence the pattern of residual beta-cell function and long-term metabolic control. *Pediatr Diabetes* 4 (1):4-9, 2003.	
LEVITT 2007 LE. Levitt Katz, A. F. J, J. Ganesh, M. Abraham, K. Murphy, and T. H. Lipman. Fasting c-peptide and insulin-like growth factor-binding protein-1 levels help to distinguish childhood type 1 and type 2 diabetes at diagnosis. *Pediatr Diabetes* 8 (2):53-59, 2007.	

Reference	Reason for exclusion
LO 2004 Fu Sung Lo, Min Hai Yang, Luan Yin Chang, Yung Chun Ou, and Yang Hau Van. Clinical features of type 1 diabetic children at initial diagnosis. *Acta Paediatr.Taiwan.* 45 (4):218-223, 2004.	
LUDVIGSSON J. Ludvigsson, A. Carlsson, G. Forsander, S. Ivarsson, I. Kockum, A. Lernmark, B. Lindblad, C. Marcus, and U. Samuelsson. C-peptide in the classification of diabetes in children and adolescents. *Pediatr Diabetes* 13 (1):45-50, 2012.	
KAAS 2012A A Kaas, MLM Andersen, S Fredheim, P Hougaard, K Buschard, JS Petersen, C de Beaufort, KJ. Robertson, L Hansen, HB. Mortensen, LB. Nielsen, and Hvidoere Study Group on Childhood Diabetes. Proinsulin, GLP-1, and glucagon are associated with partial remission in children and adolescents with newly diagnosed type 1 diabetes. *Pediatr Diabetes* 13 (1):51-58, 2012.	
ZMYSLOWSKA 2007A A. Zmyslowska, W. Mlynarski, A. Szadkowska, and J. Bodalski. Prediction of the clinical remission using the C-peptide level in type 1 diabetes in children. *Endokrynol.Diabetol.Choroby Przemiany Materii Wieku Rozwojowego* 13 (2):71-74, 2007.	
MORTENSEN 2010 HB. Mortensen, PGF. Swift, RW. Holl, P. Hougaard, L Hansen, H Bjoerndalen, CE. de Beaufort, M Knip, and Hvidoere Study Group on Childhood Diabetes. Multinational study in children and adolescents with newly diagnosed type 1 diabetes: association of age, ketoacidosis, HLA status, and autoantibodies on residual beta-cell function and glycemic control 12 months after diagnosis. *Pediatr Diabetes* 11 (4):218-226, 2010.	
PFLEGER 2008 C Pfleger, HB. Mortensen, L Hansen, C Herder, BO. Roep, H Hoey, HJ Aanstoot, M Kocova, NC. Schloot, and Hvidore Study Group on Childhood Diabetes. Association of IL-1ra and adiponectin with C-peptide and remission in patients with type 1 diabetes. *Diabetes* 57 (4):929-937, 2008.	
COPELAND 2011 K. C. Copeland, P. Zeitler, M. Geffner, C. Guandalini, J. Higgins, K. Hirst, F. R. Kaufman, B. Linder, S. Marcovina, P. McGuigan, L. Pyle, W. Tamborlane, and S. Willi. Characteristics of adolescents and youth with recent-onset type 2 diabetes: The TODAY cohort at baseline. *J.Clin.Endocrinol.Metab.* 96 (1):159-167, 2011.	
KLINGENSMITH 2010 GJ. Klingensmith, L Pyle, S Arslanian, KC. Copeland, L Cuttler, F Kaufman, L Laffel, S Marcovina, SE. Tollefsen, RS. Weinstock, B Linder, and TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. *Diabetes Care* 33 (9):1970-1975, 2010.	

Reference	Reason for exclusion
HOLMBERG 2006 H Holmberg, O Vaarala, V Sadauskaite-Kuehne, J Ilonen, Z Padaiga, and J Ludvigsson. Higher prevalence of autoantibodies to insulin and GAD65 in Swedish compared to Lithuanian children with type 1 diabetes. *Diabetes Res.Clin.Pract.* 72 (3):308-314, 2006.	
Studies in adults and young people (age <17 years) with sample size of n<50	
RODACKI 2004 M. Rodacki, L. Zajdenverg, M. S. Albernaz, M. R. Bencke-Goncalves, A. Milech, and J. E. P. Oliveira. Relationship between the prevalence of anti-glutamic acid decarboxylase autoantibodies and duration of type 1 diabetes mellitus in Brazilian patients. *Braz.J.Med.Biol.Res.* 37 (11):1645-1650, 2004.	Wrong sample size: adults and young people N<50
ASTORRI 2010 E. Astorri, C. Guglielmi, M. Bombardieri, C. Alessandri, R. Buzzetti, D. Maggi, G. Valesini, C. Pitzalis, and P. Pozzilli. Circulating Reg1alpha proteins and autoantibodies to Reg1alpha proteins as biomarkers of beta-cell regeneration and damage in type 1 diabetes. *Horm.Metab.Res.* 42 (13):955-960, 2010.	Wrong sample size: adults and young people N<50
ZHENG 2011 C Zheng, Z Zhou, L Yang, J Lin, G Huang, X Li, W Zhou, X Wang, and Z Liu. Fulminant type 1 diabetes mellitus exhibits distinct clinical and autoimmunity features from classical type 1 diabetes mellitus in Chinese. *Diabetes.Metab.Res.Rev.* 27 (1):70-78, 2011.	Wrong sample size: adults and young people N<50
MIMURA 2005 T Mimura, H Funatsu, Y Uchigata, S Kitano, E Shimizu, S Amano, S Yamagami, H Noma, M Araie, and S Hori. Glutamic acid decarboxylase autoantibody prevalence and association with HLA genotype in patients with younger-onset type 1 diabetes and proliferative diabetic retinopathy. *Ophthalmology* 112 (11):1904-1909, 2005.	Wrong sample size: adults and young people N<50
UNNIKRISHNAN 2000 AG. Unnikrishnan, V Kumaravel, V Nair, A Rao, RV. Jayakumar, H Kumar, and CB. Sanjeevi. TSH receptor antibodies in subjects with type 1 diabetes mellitus. *Ann.N.Y.Acad.Sci.* 1079:220-225, 2006.	Wrong sample size: adults and young people N<50
Studies in adults with a sample size of n<50	
YANG 2005 L Yang, Z Guang Zhou, G Huang, L Li Ouyang, X Li, and X Yan. Six-year follow-up of pancreatic beta cell function in adults with latent autoimmune diabetes. *World J Gastroenterol* 11 (19):2900-2905, 2005.	
TANKOVA 2003 T. Tankova, L. Dakovska, G. Kirilov, and D. Koev. Intravenous glucose tolerance test and anti-GAD65 antibodies in the diagnosis of the type of diabetes mellitus. *Pract.Diabetes Int.* 20 (1):13-17, 2003.	

Reference	Reason for exclusion
MILICEVIC 2004 Z. Milicevic, J. Knezevic, A. Sabioncello, G. Roglic, and B. Rocic. Beta-cell secretory function and CD25 + lymphocyte subsets in the early stage of type 1 diabetes mellitus. *Exp.Clin.Endocrinol.Diabetes* 112 (4):181-186, 2004.	
NG 2002 W. Y. Ng, K. F. Lui, J. S. Cheah, and A. C. Thai. IgG1 subclass dominates autoimmune response to tyrosine phosphatase-like molecule IA-2 in Chinese type 1 diabetes patients. *Horm.Metab.Res.* 34 (10):596-600, 2002.	
GOMEZ 2008 JM Gomez, R Vila, P Catalina, J Soler, L Badimon, and M Sahun. The markers of inflammation and endothelial dysfunction in correlation with glycated haemoglobin are present in type 2 diabetes mellitus patients but not in their relatives. *Glycoconj.J.* 25 (6):573-579, 2008.	
HUANG 2004 C.-Y. Huang and S.-M. Lai. Low prevalence of latent autoimmune diabetes in adult type 2 diabetic patients with age of onset at 30-39 years in Taiwan. *J.Intern.Med.Taiwan* 15 (1):12-18, 2004.	
KUROWSKA 2010 M. Kurowska, J. S. Tarach, J. Malicka, H. Jankowska, and A. Dabrowska. Islet GAD autoantibodies in patients with newly diagnosed type 2 diabetes. *Ann.Univ.Mariae Curie-Sklodowska Sect.DDD Pharm.* 23 (3):101-106, 2010.	

K.2 Education programmes and self-care

K.2.1 Structured education

Reference	Reason for exclusion
Studies found from literature search and cross-referencing	
BOWES 2009 A. Bowes, H. L. Painter, F. Kay, and D. Kerr. The effectiveness of a mobile phone based approach for teaching carbohydrate counting in comparison to a standard programme in Type 1 diabetes. Diabet.Med. 26:18, 2009.	Conference abstract. Already have sufficient published RCT evidence for this question.
LINETSKY2010 E Linetsky. Evaluation of the "mastering your diabetes" self management education program: Exploring the relationship between diabetes knowledge, patient self-efficacy and metabolic control. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 71 (3-B), 2010.	Dissertation abstract; study data is not an RCT
RENDERS2009 CM Renders, GD. Valk, SJ. Griffin, E Wagner, J ThM van Eijk, and J. J. Assendelft Willem. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *Cochrane Database of Systematic Reviews* Issue 4:CD001481, 2009.	Cochrane Review – wrong interventions: financial and organisational strategies aimed at improving care

Reference	Reason for exclusion
LOVEMAN2003 E. Loveman, C. Cave, C. Green, P. Royle, N. Dunn, and N. Waugh. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 7 (22):iii, 1-iii190, 2003.	HTA (2003) – already included in old NICE 2004 type 1 diabetes guideline.
VESPIANI2009 G. Vespasiani, M. C. Rossi, Bartolo P. Di, C. Sardu, D. Bruttomesso, Pos M. Dal, A. Girelli, E. Zarra, F. Ampudia, D. Kerr, A. Ceriello, C. De La Cuesta, F. Pellegrini, D. Horwitz, and A. Nicolucci. Comparison between the "Diabetes Interactive Diary" telemedicine system and standard carbohydrate counting education: an open label, international, multicentre, randomised study. *Diabetologia* 52 (S1):S388, 2009.	Abstract of a later published trial which we have already included (ROSSI 2010)
LEELARATHNA 2011 L. Leelarathna, R. Guzder, K. Muralidhara, and M. L. Evans. Diabetes: glycaemic control in type 1. *Clin Evid (Online)* 2011, 2011.	Review
SHEARER 2004 A. Shearer, A. Bagust, D. Sanderson, S. Heller, and S. Roberts. Cost-effectiveness of flexible intensive insulin management to enable dietary freedom in people with Type 1 diabetes in the UK. *Diabet.Med.* 21 (5):460-467, 2004.	Cost-effectiveness study; no clinical data/outcomes
BOREN 2009A S. A. Boren, K. A. Fitzner, P. S. Panhalkar, and J. E. Specker. Costs and benefits associated with diabetes education a review of the literature. *Diabetes Educ.* 35 (1):72-96, 2009.	SR but no meta-analysis; Mixed population (type 1 diabetes and type 2 diabetes)
PIMOUGET 2011 C. Pimouguet, Goff M. Le, R. Thiebaut, J. F. Dartigues, and C. Helmer. Effectiveness of disease-management programs for improving diabetes care: A meta-analysis. *CMAJ* 183 (2):E115-E127, 2011.	Meta-analysis with mixed population (type 1 diabetes and type 2 diabetes; mainly type 2 diabetes) and no type 1 diabetes subgroup analysis
TSHIANANGA 2012 J. K. T. Tshiananga, S. Kocher, C. Weber, K. Erny-Albrecht, K. Berndt, and K. Neeser. The effect of nurse-led diabetes self-management education on glycosylated hemoglobin and cardiovascular risk factors: A meta-analysis. *Diabetes Educ.* 38 (1):108-123, 2012.	Meta-analysis with mixed population (type 1 diabetes and type 2 diabetes; mainly type 2 diabetes). Type 1 diabetes studies in subgroup analysis were in adolescents not adults.
MANNUCCI 2005 E. Mannucci, L. Pala, and C. M. Rotella. Long-term interactive group education for type 1 diabetic patients. *Acta Diabetol.* 42 (1):1-6, 2005.	Not an RCT
JOHNSON 2010 T. M. Johnson, M. R. Murray, and Y. Huang. Associations between self-management education and comprehensive diabetes clinical care. *Diabetes Spectr.* 23 (1):41-46, 2010.	Not an RCT

Reference	Reason for exclusion
LEELARATHNA 2011A L. Leelarathna, C. Ward, K. Davenport, S. Donald, A. Housden, F. M. Finucane, and M. Evans. Reduced insulin requirements during participation in the DAFNE (dose adjustment for normal eating) structured education programme. *Diabetes Res.Clin.Pract.* 92 (2):e34-e36, 2011.	DAFNE study – wrong outcomes: insulin dose
GUNN 2012 D. Gunn and P. Mansell. Glycaemic control and weight 7 years after Dose Adjustment For Normal Eating (DAFNE) structured education in Type 1 diabetes. *Diabetes Medicine* 29 (6):807-812, 2012.	DAFNE study 7 year results – wrong comparison group: age-matched controls rather than original randomised groups.
SPEIGHT 2010 J. Speight, S. A. Amiel, C. Bradley, S. Heller, L. Oliver, S. Roberts, H. Rogers, C. Taylor, and G. Thompson. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled Type 1 diabetes. *Diabetes Res.Clin.Pract.* 89 (1):22-29, 2010.	DAFNE study 4 year results– wrong follow-up time for correct comparison group: data is given after both groups have had DAFNE not DAFNE vs no DAFNE
ALBANO 2008 M. G. Albano, C. Crozet, and J. F. d'Ivernois. Analysis of the 2004-2007 literature on therapeutic patient education in diabetes: results and trends. *Acta Diabetol.* 45 (4):211-219, 2008.	SR but no meta-analysis
STEUTEN 2007 L. M. Steuten, H. J. Vrijhoef, S. Landewe-Cleuren, N. Schaper, G. G. Van Merode, and C. Spreeuwenberg. A disease management programme for patients with diabetes mellitus is associated with improved quality of care within existing budgets (Provisional abstract). *Diabet.Med.* 24 (10):1112-1120, 2007.	Mixed population (type 1 diabetes and type 2 diabetes, <75% type 1 diabetes – 3%) and no type 1 diabetes subgroup analysis
SIMMONS 2004 D. Simmons, G. D. Gamble, S. Foote, D. R. Cole, and G. Coster. The New Zealand Diabetes Passport Study: A randomized controlled trial of the impact of a diabetes passport on risk factors for diabetes-related complications. *Diabet.Med.* 21 (3):214-217, 2004.	Mixed population (type 1 diabetes and type 2 diabetes; <75% type 1 diabetes – 25%) and no type 1 diabetes subgroup analysis
NEBEL 2004 I. T. Nebel, T. Klemm, M. Fasshauer, U. Müller, H. J. Verlohren, A. Klaiberg, and R. Paschke. Comparative analysis of conventional and an adaptive computer-based hypoglycaemia education programs. *Patient Educ.Couns.* 53 (3):315-318, 2004.	Mixed population (type 1 diabetes and type 2 diabetes; <75% type 1 diabetes – 38%) and no type 1 diabetes subgroup analysis
POLONSKY 2005 W. H. Polonsky, J. Zee, M. A. Yee, M. A. Crosson, and R. A. Jackson. A community-based program to encourage patients' attention to their own diabetes care: Pilot development and evaluation. *Diabetes Educ.* 31 (5):691-699, 2005.	Mixed population (type 1 diabetes and type 2 diabetes; <75% type 1 diabetes – 2%) and no type 1 diabetes subgroup analysis
CARLONE 2011	Abstract of presentation

Reference	Reason for exclusion
A. Carlone, L. Cipolloni, G. Gillanti, C. Gnessi, G. Leto, and R. Buzzetti. Effectiveness of therapeutic-educational re-training in patients affected by type 1 diabetes treated with CSII (continuous subcutaneous insulin infusion). *Diabetologia* 54:S33, 2011.	on education re-training
DINNEEN 2009 S. F. Dinneen, M. C. O' Hara, M. Byrne, J. Newell, L. Daly, D. O' Shea, D. Smith, and Irish DAFNE Study Group. The Irish DAFNE study protocol: a cluster randomised trial of group versus individual follow-up after structured education for type 1 diabetes. *Trials* 10:88, 2009.	IRISH DAFNE – Protocol of study design, not results. [RO: Trial will be completed in 2012 so hopefully results published in 2013 for reruns]
DINNEEN 2009A S. F. Dinneen, M. O'Hara, J. Newell, and M. Byrne. Evaluating self-management support in type 1 diabetes: design and baseline data from the Irish Dose Adjustment for Normal Eating (DAFNE) Study. *Diabetologia* 52 (S1):S389, 2009.	IRISH DAFNE - Abstract of design and baseline characteristics, not results.
DINNEEN 2011 S. F. Dinneen, M. O'Hara, J. Newell, N. Coffey, D. O'Shea, D. Smith, H. Courtney, C. McGurk, M. O'Scannail, and C. Breen. Group follow-up compared to individual clinic follow-up after structured education for type 1 diabetes: the Irish DAFNE Study. *Ir.J.Med.Sci.* 180:S504, 2011.	Abstract. Wrong intervention: follow-up methods after IRISH DAFNE programme
HEALTH 2011 Technology Assessment Health. The REPOSE (Relative Effectiveness of Pumps Over MDI and Structured Education) trial (Project record). *Health Technol.Assess.*, 2011.	REPOSE TRIAL – Overview of trial progress (education + pump treatment vs. education + needle multiple injection)
COCHRAN 2009 J Cochran and VS. Conn. Meta-analysis of quality of life outcomes following diabetes self-management training. *The Diabetes Educator* 34 (5):815-823, 2009.	Mixed population (type 1 diabetes and type 2 diabetes; mainly type 2 diabetes) and no type 1 diabetes subgroup analysis
BRAZEAU 2011 A.-S. Brazeau, K. Desjardins, C. Suppere, P. Briand, H. Mircescu, and R. Rabasa-Lhoret. Physical activity promotion in adults with type 1 diabetes: The PAP-1 pilot program. *Diabetes* 60:A576, 2011.	Abstract of PAP-1 pilot trial (physical activity promotion)
WEINGER 2011 K. Weinger, E. A. Beverly, Y. Lee, L. Sitnokov, O. P. Ganda, and A. E. Caballero. The effect of a structured behavioral intervention on poorly controlled diabetes: a randomized controlled trial. *Arch.Intern.Med.* 171 (22):1990-1999, 2011.	Mixed population (type 1 diabetes and type 2 diabetes, <75% type 1 diabetes – 50%) and no type 1 diabetes subgroup analysis
BENHAMOU 2010 P. Y. Benhamou, C. Garnier, I. Debaty, A. Rueff, C. Gilbert, M. Ressel, C. Siaud, E. Boudrot, B. Carpentier, R. Boizel, L. Nasse, and S. Halimi. Basal insulin dose in 40 type 1 diabetic patients remains stable 1 year after educational training in flexible insulin therapy. *Diabetes Metab.* 36 (5):369-374, 2010.	Not an RCT; inulin treatment education programme (before-and-after)

Reference	Reason for exclusion
POLONSKY 2003 W. H. Polonsky, J. Earles, S. Smith, D. J. Pease, M. Macmillan, R. Christensen, T. Taylor, J. Dickert, and R. A. Jackson. Integrating medical management with diabetes self-management training: a randomized control trial of the Diabetes Outpatient Intensive Treatment program. *Diabetes Care* 26 (11):3048-3053, 2003.	Mixed population (type 1 diabetes and type 2 diabetes; <75% type 1 diabetes – 14%) and no type 1 diabetes subgroup analysis
SCHIEL 2006A R. Schiel, U. Voigt, I. S. Ross, A. Braun, A. Rillig, W. Hunger-Dathe, G. Stein, and U. A. Muller. Structured diabetes therapy and education improves the outcome of patients with insulin treated diabetes mellitus. The 10 year follow-up of a prospective, population-based survey on the quality of diabetes care (the JEVIN Trial). *Exp.Clin.Endocrinol.Diabetes* 114 (1):18-27, 2006.	JEVIN trial: not an RCT
THOMPSON 2011 G. Thompson and C. D. Taylor. Structured diabetes education: Developing active user involvement. *Diabet.Med.* 28:120, 2011.	Abstract about DAFNE user action group (wrong intervention)
HERMANNS 2010 N. Hermanns, B. Kulzer, M. Krichbaum, T. Kubiak, and T. Haak. Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 33 (3):e36, 2010.	Letter about HyPOS trial; the main trial has already been included in the review
IZQUIERDO 2003 R. E. Izquierdo, P. E. Knudson, S. Meyer, J. Kearns, R. Ploutz-Snyder, and R. S. Weinstock. A comparison of diabetes education administered through telemedicine versus in person. *Diabetes Care* 26 (4):1002-1007, 2003.	Mixed population (type 1 diabetes and type 2 diabetes; <75% type 1 diabetes – 11%) and no type 1 diabetes subgroup analysis
BRUTTOMESSO 2006 D. Bruttomesso, S. Costa, Pos M. Dal, D. Crazzolara, G. Realdi, A. Tiengo, A. Baritussio, and R. Gagnayre. Educating diabetic patients about insulin use: Changes over time in certainty and correctness of knowledge. *Diabetes Metab.* 32 (3):256-261, 2006.	Not an RCT
GEORGE 2007 J. T. George, A. P. Valdovinos, J. C. Thow, I. Russell, P. Dromgoole, S. Lomax, D. J. Torgerson, and T. Wells. Brief intervention in type 1 diabetes - Education for self-efficacy (BITES): Protocol for a randomised control trial to assess biophysical and psychological effectiveness. *BMC Endocrine Disorders* 7:6TN, 2007.	Protocol for BITES study (BITES study already include in review)
BOWES 2009 A. Bowes, H. L. Painter, F. Kay, and D. Kerr. The effectiveness of a mobile phone based approach for teaching carbohydrate counting in comparison to a standard programme in Type 1 diabetes. *Diabet.Med.* 26:18, 2009.	Abstract only. Mobile phone based approach for teaching CHO counting vs. standard programme
TAYLOR 2012 C. D. Taylor, H. Rogers, C. Ward, J. Carling, D. Kitchener, and L. Oliver. Development and piloting of a structured education curriculum for insulin pump therapy prior to the REPOSE (Relative Effectiveness of Pumps over MDI	Abstract only. Not RCT. Adapted DAFNE curriculum for CSII (pump therapy).

Reference	Reason for exclusion
with Structured Education) trial. *Diabet.Med.* 29:104, 2012.	
KUBIAK 2006A T. Kubiak, N. Hermanns, H. J. Schreckling, B. Kulzer, and T. Haak. Evaluation of a self-management-based patient education program for the treatment and prevention of hypoglycemia-related problems in type 1 diabetes. *Patient Educ.Couns.* 60 (2):228-234, 2006.	Not designed as an RCT, pts assigned not randomised.
POWELL 2006 M. F. Powell, V. D. Burkhart, and P. P. Lamy. Diabetic patient compliance as a function of counseling. Ann.Pharmacother. 40 (4):747-752, 2006.	Not designed as an RCT, pts assigned not randomised.
DINEEN 2013 SF. Dinneen, Mary Clare O'Hara, Molly Byrne, Diarmuid Smith, Christopher H. Courtney, Colm McGurk, Simon R. Heller, John Newell, Norma Coffey, Cathy Breen, Mary O'Scannail, Donal O'Shea, and Irish DAFNE Study Group. Group follow-up compared to individual clinic visits after structured education for type 1 diabetes: a cluster randomised controlled trial. *Diabetes Res.Clin.Pract.* 100 (1):29-38, 2013.	Follow-up education after original DAFNE programme
BATTISTA 2012 M. C. Battista, M. Labonte, J. Menard, F. Jean-Denis, G. Houde, J. L. Ardilouze, and P. Perron. Dietitian-coached management in combination with annual endocrinologist follow up improves global metabolic and cardiovascular health in diabetic participants after 24 months. *Appl.Physiol.Nutr.Metab.* 37 (4):610-620, 2012.	Wrong intervention: dietician follow-up + education (nutrition only – not full diabetes structured education programme). Wrong population: mixed population of type 1 diabetes and type 2 diabetes.
KRUGER 2013 J. Kruger, A. Brennan, P. Thokala, H. Basarir, R. Jacques, J. Elliott, S. Heller, and J. Speight. The cost-effectiveness of the Dose Adjustment for Normal Eating (DAFNE) structured education programme: An update using the Sheffield Type 1 Diabetes Policy Model. *Diabet.Med.* 30 (10):1236-1244, 2013.	No new clinical data – based on studies already included in our review.
PEREIRA 2012 DA Pereira, Nilce Maria da Silva Campos Costa, Ana Luiza Lima Sousa, Paulo Cesar Brandao Veiga Jardim, and Claudia Regina de Oliveira Zanini. The effect of educational intervention on the disease knowledge of diabetes mellitus patients. *Rev.Lat.Am.Enfermagem* 20 (3):478-485, 2012.	Wrong population: type 2 diabetes
ROSSI 2012 M. C. Rossi, A. Nicolucci, G. Lucisano, Bartolo P. Di, V. Miselli, R. Anichini, and G. Vespasiani. "Diabetes Interactive Diary" Telemedicine System vs. Standard Carbohydrate Counting Education in Type 1 Diabetes: Results of a randomized trial. *Diabetes* 61:A292, 2012.	Conference abstract.
SUN 2012 AC. Sun, Janice Y. Tsoh, Anne Saw, Joanne L. Chan, and Joyce W. Cheng. Effectiveness of a culturally tailored diabetes self-management program for Chinese Americans. *Diabetes Educ.* 38 (5):685-694, 2012.	Mixed population of type 1 diabetes and type 2 diabetes; not give % type 1 diabetes and no type 1 diabetes subgroup

Reference	Reason for exclusion
	analysis. Culturally-tailored education – not applicable to UK general population.
RAHMANI 2013 G. S. Rahmani, M. C. O'Hara, M. Byrne, J. Newell, and S. F. Dinneen. Impact of severe hypoglycaemia on healthrelated quality of life and psychological wellbeing before and after participation in a structured education programme for people with Type 1 diabetes in Ireland. *Diabet.Med.* 30:134, 2013.	Conference abstract – already got enough fully published evidence. Not an RCT.
KULZER 2012 B. Kulzer, N. Hermanns, D. Ehrmann, N. Bergis, and T. Haak. The effect of a self-management oriented education and treatment programme (PRIMAS) for type 1 diabetic patients. *Diabetologia* 55:S408, 2012.	Conference abstract – already got enough fully published evidence; study now published in full and included in our review (HERMANNS 2013).
KULZER 2013 B. Kulzer, N. Hermanns, D. Ehrmann, N. B. Jurgan, and T. Haak. The effect of a diabetes education programme (primas) for people with type 1 diabetes: results of a randomized trial. *Diabetes* 62:A79-A80, 2013.	Conference abstract – already got enough fully published evidence; study now published in full and included in our review (HERMANNS 2013).
KRUGER 2013A J. Kruger, A. Brennan, P. Thokala, H. Basarir, R. Jacques, and J. Elliott. The cost-effectiveness of five week vs one week DAFNE structured education in Type 1 diabetes: A preliminary evaluation using the Sheffield Type 1 diabetes policy model. *Diabet.Med.* 30:131, 2013.	Conference abstract now published (KRUGER 2013 which has been excluded from our review). Cost-effectiveness study.
BEVERLY 2012 E. A. Beverly, Y. Lee, O. P. Ganda, M. Munshi, A. E. Caballero, and K. Weinger. Do older patients benefit from group diabetes education? *Diabetes* 61:A167, 2012.	Conference abstract – already got enough fully published evidence; study now published in full and included in our review (BEVERLY 2013).
HOPKINS 2012 D. Hopkins, I. Lawrence, P. Mansell, G. Thompson, S. Amiel, M. Campbell, and S. Heller. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care* 35 (8):1638-1642, 2012.	Not RCT; audit data of DAFNE education programme.
DEZOYSA 2014 N. de Zoysa, H. Rogers, M. Stadler, C. Gianfrancesco, S. Beveridge, E. Britneff, P. Choudhary, J. Elliott, S. Heller, and S. A. Amiel. A Psychoeducational Program to Restore Hypoglycemia Awareness: The DAFNE-HART Pilot Study. *Diabetes Care* 37 (3):863-866, 2014.	Not RCT.
BEVERLY 2013 EA. Beverly, Shane Fitzgerald, Lilya Sitnikov, Om P. Ganda, A. Enrique Caballero, and Katie Weinger. Do older adults aged 60-75 years benefit from diabetes behavioral interventions? *Diabetes Care* 36 (6):1501-1506, 2013.	Mixed population of type 1 diabetes and T2d (<70% type 1 diabetes and no specific type 1 diabetes subgroup analysis). Subgroup analysis done is

Reference	Reason for exclusion
	by age and type of diabetes mixed together, so unable to get type 1 diabetes specific data.
GARDNER 2014 Gardner KJ, Jacques RM, Hopkinson HE. Influence of basal insulin (BI) regimen on outcome after structured education in adults with Type 1 diabetes in a Scottish diabetes service. Diabetic Medicine. 2014; 31:97	Conference abstract
HERNANDEZ 2014 Hernandez RMS, Plasencia YL, Martel DA, Cordero JR, Ortega AJ, Dominguez AC et al. Preliminary evaluation of the ANAIS education programme for type 1 diabetes (T1D): A randomised controlled trial. Diabetes. 2014; 63:A172	Conference abstract
HOPKINSON 2014 Hopkinson HE, Jacques RM, Gardner KJ, Amiel SA, Mansell PM. A twice daily basal insulin (BI) replacement regimen achieves better glycaemic control than a once daily regimen during structured education in adults with Type 1 diabetes in routine UK clinical practice. Diabetic Medicine. 2014; 31:7	Conference abstract
Studies suggested by gdg members	
SCHIEL 2006A R. Schiel, U. Voigt, I. S. Ross, A. Braun, A. Rillig, W. Hunger-Dathe, G. Stein, and U. A. Muller. Structured diabetes therapy and education improves the outcome of patients with insulin treated diabetes mellitus. The 10 year follow-up of a prospective, population-based survey on the quality of diabetes care (the JEVIN Trial). *Exp.Clin.Endocrinol.Diabetes* 114 (1):18-27, 2006.	Already excluded: not an RCT (Jevin study)
PIEBER 1995 T. R. Pieber, G. A. Brunner, W. J. Schnedl, S. Schattenberg, P. Kaufmann, and G. J. Krejs. Evaluation of a structured outpatient group education program for intensive insulin therapy. *Diabetes Care* 18 (5):625-630, 1995.	Not an RCT: before and after study (structured diabetes teaching and treatment program (DTTP)
PLANK 2004 J. Plank, G. Kohler, I. Rakovac, B. M. Semlitsch, K. Horvath, G. Bock, B. Kraly, and T. R. Pieber. Long-term evaluation of a structured outpatient education programme for intensified insulin therapy in patients with Type 1 diabetes: a 12-year follow-up. *Diabetologia* 47 (8):1370-1375, 2004.	Not an RCT: before and after study (structured diabetes teaching and treatment program (DTTP) – 12 year follow-up of the Pieber 1995 study.
BOTT 2000 U. Bott, S. Bott, D. Hemmann, and M. Berger. Evaluation of a holistic treatment and teaching programme for patients with Type 1 diabetes who failed to achieve their therapeutic goals under intensified insulin therapy. *Diabet Med* 17 (9):635-643, 2000.	Not an RCT: before and after study (teaching and treatment programme).
SAMANN 2005 A. Samann, I. Muhlhauser, R. Bender, Ch Kloos, and U. A. Muller. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 48 (10):1965-1970, 2005.	Not an RCT: before and after study (Implementation study of DAFNE).

Reference	Reason for exclusion
SAMANN 2006 A. Samann, I. Muhlhauser, R. Bender, W. Hunger-Dathe, C. Kloos, and U. A. Muller. Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis. *Diabetes Care* 29 (10):2196-2199, 2006.	Not an RCT: before and after study. Diabetes treatment and teaching programs (DTTPs) for type 1 diabetes
HOPKINS 2012 D. Hopkins, I. Lawrence, P. Mansell, G. Thompson, S. Amiel, M. Campbell, and S. Heller. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care* 35 (8):1638-1642, 2012.	Not an RCT: audit.
SCHMIDT 2012 S Schmidt, M Meldgaard, N Serifovski, C Storm, TM Christensen, B Gade-Rasmussen, and K Norgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care 35 (5):984-990, 2012.	The education component was only 1 x 3hr group teaching session, so cannot be classed as a 'structured education programme'.

K.2.2 Carb counting

Reference	Reason for exclusion
ANDERSON 1993 E. J. Anderson, M. Richardson, G. Castle, S. Cercone, L. Delahanty, R. Lyon, D. Mueller, and L. Snetselaar. Nutrition interventions for intensive therapy in the Diabetes Control and Complications Trial. The DCCT Research Group. *J.Am.Diet.Assoc.* 93 (7):768-772, 1993.	Overview of DCCT and case studies
BLAZIK 2009 M. Blazik, A. Szypowska, D. Golicka, L. Groele, and E. Pankowska. The "diabetics" software in adjusting prandial insulin in patients treated with insulin pumps. the results of RCT study. *Pediatr.Diabetes* 10:71, 2009.	Conference abstract. Wrong population: children. Technology of CHO count vs. manual CHO count.
BRANDMILLER 2011 J. C. Brand-Miller, J. Bao, H. R. Gilbertson, R. Gray, D. Munns, G. Howard, P. Petocz, and S. Colagiuri. Improving the estimation of mealtime insulin dose in adults with type 1 diabetes: Normal Insulin Demand for Dose Adjustment (NIDDA study). *Diabetologia* 54:S400, 2011.	Conference abstract. Study now published (BAO 2011) and included in this review.
CARSTENSEN 2010 S. Carstensen, J. W. Huber, M. Schonauer, and A. Thomas. Effects of evening meals with complex nutrient content on the nocturnal blood glucose levels of type 1 diabetes patients. *Diabetologia* 53:S403-S404, 2010.	Conference abstract. Wrong comparisons: CHO counting vs. CHO + protein + fat counting. Only test meals not long term. Wrong outcomes (post-prandial glucose)
CHARPENTIER 2011 Charpentier G, Benhamou PY, Dardari D, Clergeot A, Franc S, Schaepelynck-Belicar P et al. The Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support improves HbA1c in poorly controlled type 1 diabetic	Considered for CC alone vs bolus calculator + CC (reported groups G1 & G2). Intervention is not a bolus calculator alone (also calculates adjustments in CHO ratio, basal insulin dose or pump rates if SMBG

Reference	Reason for exclusion
patients: a 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes Care. 2011; 34(3):533-539.	does not meet target)
DAVIDSON 2008 P C. Davidson, H R. Hebblewhite, R D. Steed, and B W. Bode. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocr Pract* 14 (9):1095-1101, 2008.	Mathematical models for CHO-insulin ratio counting.
DOMINGUEZ 2011 Dominguez-Lopez ME, Ruiz De Adana MS, Gonzalez-Molero I, Guerrero M, Cardona I, Sanchez I et al. Clinical usefulness of a bolus calculator in patients with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion (CSII). Diabetes Technology and Therapeutics. 2011; 13(2):219.	Conference abstract.
FRANZ 2003 M J. Franz. Adjusting mealtime insulin based on meal carbohydrate content improves glycemic control and quality of life. *Curr Diab Rep* 3 (5):395-396, 2003.	Overview of DAFNE.
GARCIALOPEZ 2013 J M Garcia-Lopez, M Gonzalez-Rodriguez, M Pazos-Couselo, F Gude, A Prieto-Tenreiro, and F Casanueva. Should the amounts of fat and protein be taken into consideration to calculate the lunch prandial insulin bolus? Results from a randomized crossover trial. *Diabetes Technol.Ther.* 15 (2):166-171, 2013.	Does not answer the question: effect of fat and protein content in meals (CHO counting method in test meals with same CHO content but different protein/fat content)
GONZALEZRODRIGUEZ 2010 M. Gonzalez-Rodriguez, A. Prieto-Tenreiro, M. Pazos-Couselo, P. Andujar-Plata, R. Villar-Taibo, D. Peteiro-Gonzalez, C. Guillin-Amarelle, F. F. Casanueva-Freijo, and J. Garcia-Lopez. Should the amount of fat and protein be taken into consideration to calculate preprandial insulin bolus? *Diabetologia* 53:S404, 2010.	Conference abstract. Study now published (GARCIALOPEZ 2013) and excluded in this review.
HEGAR 2011 K Hegar, S Heiber, M Brandle, E Christ, and U Keller. Carbohydrate counting of food. *Swiss Med Wkly* 141:w13224, 2011.	Wrong comparisons: different method for teaching CHO counting (tools to assess the patient's ability to CHO count).
KALERGIS 2000 Kalergis M, Pacaud D, Strychar I, Meltzer S, Jones PJ, Yale JF. Optimizing insulin delivery: assessment of three strategies in intensive diabetes management. Diabetes, Obesity and Metabolism. 2000; 2(5):299-305.	Wrong intervention: compared carb counting with meal food exchange. Carb count group also had qualitative adjustment of insulin for exercise and stress
KAUFMAN 1999 F. R. Kaufman, M. Halvorson, and S. Carpenter. Use of a plastic insulin dosage guide to correct blood glucose levels out of the target range and for carbohydrate counting in subjects with type 1 diabetes. *Diabetes Care* 22 (8):1252-1257, 1999.	Wrong population: children.

Reference	Reason for exclusion
LOWE 2008 J. Lowe, S. Linjawi, M. Mensch, K. James, and J. Attia. Flexible eating and flexible insulin dosing in patients with diabetes: Results of an intensive self-management course. *Diabetes Res.Clin.Pract.* 80 (3):439-443, 2008.	Wrong population: mix of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis and <70% type 1 diabetes. Wrong intervention: education course.
MAURIZI 2010 A. Maurizi, A. Palermo, Anguissola G. Beretta, D. Benevento, A. Lauria, E. Cipponeri, D. Tuccinardi, S. Manfrini, and P. Pozzilli. A pocket instrument for calculating insulin need in the management of type 1 diabetes. *Diabetologia* 53:S386-S387, 2010.	Conference abstract. Study now published (MAURIZI 2011)
OSWALD 2004 G. Oswald, A. Kinch, and E. Ruddy. Transfer to a patient centred, carbohydrate counting and insulin matching programme in a shortened time frame. *Pract.Diabetes Int.* 21 (9):334-338, 2004.	Wrong intervention: education programme (and no comparison).
PANKOWSKA 2012 Pankowska E, Blazik M, Groele L. Does the fat-protein meal increase postprandial glucose level in type 1 diabetes patients on insulin pump: the conclusion of a randomized study. Diabetes Technology and Therapeutics. 2012; 14(1):16-22.	Wrong population: children.
PELZER 2011 Ruaan Pelzer, Edward H. Mathews, and Leon Liebenberg. Preliminary application of a new bolus insulin model for type 1 diabetes. Diabetes Technol.Ther. 13 (5):527-535, 2011.	Considered for CC alone vs bolus calculator + CC. Not addressing question. New alternative to CHO counting also taking into account the metabolic efficiency of the type of CHO and person-specific absorption efficiency not just the CHO mass.
RABASALHORET 1999 R. Rabasa-Lhoret, J. Garon, H. Langelier, D. Poisson, and J. L. Chiasson. Effects of meal carbohydrate content on insulin requirements in type 1 diabetic patients treated intensively with the basal-bolus (ultralente-regular) insulin regimen. *Diabetes Care* 22 (5):667-673, 1999.	Wrong comparisons: effects of two different CHO content meals and pts ability to correctly count CHOs.
RAMOTOWSKA 2013 Ramotowska A, Golicki D, Dzygalo K, Szypowska A. The effect of using the insulin pump bolus calculator compared to standard insulin dosage calculations in patients with type 1 diabetes mellitus - systematic review. Experimental and Clinical Endocrinology and Diabetes. 2013; 121(5):248-254.	Systematic review. Intervention does not match protocol, intervention is bolus calculator carb counting but comparison is mix of carb counting and no carb counting
ROSSI 2010 M. C. Rossi, A. Nicolucci, Bartolo P. Di, D. Bruttomesso, A. Girelli, F. J. Ampudia, D. Kerr, A. Ceriello, Cde L. Mayor, F. Pellegrini, D. Horwitz, and G. Vespasiani. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. *Diabetes Care* 33 (1):109-115, 2010.	Wrong intervention: telemedicine (not carb counting telemedicine alone).

Reference	Reason for exclusion
ROSSI 2012 M. C. Rossi, A. Nicolucci, G. Lucisano, Bartolo P. Di, V. Miselli, R. Anichini, and G. Vespasiani. "Diabetes Interactive Diary" Telemedicine System vs. Standard Carbohydrate Counting Education in Type 1 Diabetes: Results of a randomized trial. *Diabetes* 61:A292, 2012.	Wrong intervention: telemedicine (not carb counting telemedicine alone).
ROSSI 2013 MC Rossi, A Nicolucci, G Lucisano, F Pellegrini, P Di Bartolo, V Miselli, R Anichini, and G Vespasiani On Behalf Of The Did Study Group. Impact of the "diabetes interactive diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. *Diabetes Technol.Ther.* 15 (8):670-679, 2013.	Wrong intervention: telemedicine (not carb counting telemedicine alone).
SCHREZENMEIR 1985 J. Schrezenmeir, H. Achterberg, J. Bergeler, E. Kustner, W. Stumer, H. Hutten, and J. Beyer. Controlled study on the use of hand-held insulin dosage computers enabling conversion to and optimizing of meal-related insulin therapy regimens. *Life Support Syst* 3 Suppl 1:561-567, 1985.	Very old study of an old technology for CHO counting.
SCHREZENMEIR 2002 Schrezenmeir J, Dirting K, Papazov P. Controlled multicenter study on the effect of computer assistance in intensive insulin therapy of type 1 diabetics. Computer Methods and Programs in Biomedicine. 2002; 69(2):97-114.	Considered for CC alone vs bolus calculator + CC. Not addressing question. Pocket computer to aid intensive insulin therapy not carb counting alone
TRENTO 2010 M. Trento, A. Trinetta, C. Kucich, S. Gamba, G. Grassi, P. Passera, M. Raballo, J. Sicuro, M. Trevisan, L. Charrier, F. Cavallo, and M. Porta. [Carbohydrate counting improves coping ability and metabolic control in patients with type 1 diabetes managed by Group Care] TO: Miglioramento delle strategie di coping, qualita di vita e controllo metabolico in persone con diabete di tipo 1 seguite mediante Group Care e conta dei carboidrati LA: Ita. *Giornale Italiano di Diabetologia e Metabolismo* 30 (4):165-171, 2010.	Not in English (and same study as TRENTO 2011).
TRENTO 2011 M. Trento, A. Trinetta, C. Kucich, G. Grassi, P. Passera, S. Gennari, V. Paganin, S. Tedesco, L. Charrier, F. Cavallo, and M. Porta. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes managed by Group Care. *J.Endocrinol.Invest.* 34 (2):101-105, 2011.	Wrong intervention: education programme (and no comparison).
VESPASIANI 2009 G. Vespasiani, M. C. Rossi, Bartolo P. Di, C. Sardu, D. Bruttomesso, Pos M. Dal, A. Girelli, E. Zarra, F. Ampudia, D. Kerr, A. Ceriello, C. De La Cuesta, F. Pellegrini, D. Horwitz, and A. Nicolucci. Comparison between the "Diabetes Interactive Diary" telemedicine system and standard carbohydrate counting education: an open label,	Conference abstract. Study now published (ROSSI 2010) and excluded in this review.

Reference	Reason for exclusion
international, multicentre, randomised study. *Diabetologia* 52 (S1):S388, 2009.	
BELL 2014 KJ. Bell, Alan W. Barclay, Peter Petocz, Stephen Colagiuri, and Jennie C. Brand-Miller. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2 (2):133-140, 2014.	Article unavailable.
SOUTO 2014 D. L. Souto, L. Zajdenverg, M. Rodacki, and E. L. Rosado. Impact of advanced and basic carbohydrate counting methods on metabolic control in patients with type 1 diabetes. *Nutrition* 30 (3):286-290, 2014.	Wrong population: mixed population of young people and adults.
BELL 2014 K. J. Bell, R. Gray, D. Munns, G. Howard, S. Colagiuri, and J. C. Brand-Miller. Food Insulin Index (FII) vs. traditional carbohydrate counting for glycemic control in adults with type 1 diabetes: A 3-month pilot study. *Diabetes* 63:A189, 2014.	Conference abstract
FORDE 2013 H. Forde, M. C. Durkan, and H. Clarke. Evaluation of a real-time carbohydrate counting course during a clinic setting in the management of diabetes type 1. *Diabetologia* 56:S424, 2013.	Conference abstract
RYDER 2013 J. Ryder, D. A. Cavan, R. Ziegler, I. Cranston, K. Barnard, C. Vogel, W. Koehler, B. Petersen, I. Vesper, K. Friedman, M. A. Schweitzer, and R. S. Wagner. Use of an automated bolus advisor may improve carbohydrate counting competence in patients treated with multiple daily insulin injection therapy: Results from ABACUS. *Diabetologia* 56:S425, 2013.	Conference abstract
SCHMIDT 2014 S. Schmidt, B. Schelde, and K. Norgaard. Effects of advanced carbohydrate counting in patients with Type 1 diabetes: a systematic review. *Diabet Med* 31 (8):886-896, 2014.	SR/MA – ued as source of references.
SCHMIDT 2013 S. Schmidt, M. Meldgaard, N. Serifovski, C. Storm, B. Gade-Rasmussen, and K. Norgaard. Long-term use of an automated bolus calculator in type 1 diabetes. *Diabetes Technol Ther* 15:A90, 2013.	Conferemce abstract
SCHMIDT 2012A S. Schmidt, M. Meldgaard, N. Serifovski, C. Storm, T. M. Christensen, B. Gade-Rasmussen, and K. Nørgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. *Diabetes care* 35 (5):984-990, 2012.	Already found study in pre-rerun literature. Has been included in the review.

K.2.3 Glycaemic index diet

Reference	Reason for exclusion
ANDERSON 1991 Anderson JW, Zeigler JA, Deakins DA, Floore TL, Dillon DW, Wood CL et al. Metabolic effects of high-carbohydrate, high-fiber diets for insulin-dependent diabetic individuals. American Journal of Clinical Nutrition. 1991; 54(5):936-943	Diet intervention given in hospital, not self-management

Reference	Reason for exclusion
ANDERSON 2004 Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. Journal of the American College of Nutrition. 2004; 23(1):5-17	SR – used as source of refs
ANON 1992 ANON. Lipid and lipoprotein levels in patients with IDDM diabetes control and complication. Trial experience. The DCCT Research Group. Diabetes Care. 1992; 15(7):886-894	Does not address diets
AUGUSTIN 2014 Augustin L, Cozma A, De SR, Sievenpiper J, Blanco-Mejia S, Li S et al. The acute effects of dietary pulses on postprandial glycemia in diabetes: A meta-analysis. FASEB Journal. 2014; 28(1 SUPPL. 1)	Conference abstract of meta-analysis; too new for full publication
AXELSEN 1999 Axelsen M, Wesslau C, Lonnroth P, Arvidsson LR, Smith U. Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycaemia in intensively treated type 1 diabetes subjects. Journal of Internal Medicine. 1999; 245(3):229-236	Wrong intervention – cornstarch supplement at bedtime, not GI diet throughout the day
BANTLE 1983 Bantle JP, Laine DC, Castle GW, Thomas JW, Hoogwerf BJ, Goetz FC. Postprandial glucose and insulin responses to meals containing different carbohydrates in normal and diabetic subjects. New England Journal of Medicine. 1983; 309(1):7-12	Wrong outcome: follow-up time too short (240 mins)
BRAND 1991 Brand JC, Colagiuri S, Crossman S, Allen A, Roberts DCK, Truswell AS. Low-Glycemic Index Foods Improve Long-Term Glycemic Controls in NIDDM. Diabetes Care. 1991; 14 (2):95-101	Wrong population: type 2 diabetes
BRAND-MILLER 2002 Brand-Miller JC, Holt SHA, Pawlak DB, McMillan J. Glycemic index and obesity. American Journal of Clinical Nutrition. 2002; 76(1):281S-285S	SR/MA – used as a source of references
BRAND-MILLER 2003 Brand-Miller J, Petocz P, Hayne S, Colagiuri S. Low- Glycemic Index Diets in the Management of Diabetes. A meta-analysis of randomized controlled trials. Diabetes Care. 2003; 26 (8):2261-2267	Meta-analysis of Type 1 and 2 diabetes. Studies cross checked
BURKE 2009 Burke GW, Ciancio G, Gaynor JJ, Sageshima J, Chen L, Rosen A et al. Lower rate of acute rejection with rapamycin vs. mycophenolate mofetil in simultaneous pancreas-kidney transplant recipients: 8-Year Follow-Up. American Journal of Transplantation. 2009; 9:216	Conference abstract. Wrong treatment – not diets
BUYKEN 2000 Buyken AE, Heitkamp G, Irsigler K, Holler C, Stehle P, Fuller JH et al.	Does not give a clear link between GI and the food

Reference	Reason for exclusion
Carbohydrate sources and glycaemic control in type 1 diabetes mellitus. Diabetic Medicine. 2000; 17(5):351-359	categories
CHEN 1993 Chen YD, Swami S, Skowronski R, Coulston AM, Reaven GM. Effect of variations in dietary fat and carbohydrate intake on postprandial lipemia in patients with noninsulin dependent diabetes mellitus. Journal of Clinical Endocrinology and Metabolism. 1993; 76(2):347-351	Wrong population: type 2 diabetes
COLLIER 1988 Collier G, Gludici S, Kalmusky J, Wolever T, Helman G, Wesser V et al. Low glycaemic index starchy foods improve glucose control and lower serum cholesterol in diabetic children. Diab Nutr Metab. 1988; 11-18	Non-adult population
DELAHANTY 2009 Delahanty LM, Nathan DM, Lachin JM, Hu FB, Cleary PA, Ziegler GK et al. Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. American Journal of Clinical Nutrition. 2009; 89(2):518-524	Not GI diets
FISCHMAN 2008 Fischman D, Nookala VK. Cystic fibrosis-related diabetes mellitus: Etiology, evaluation, and management. Endocrine Practice. 2008; 14(9):1169-1179	Wrong treatment and population – not diets.
FONTVIEILLE 1988 Fontvieille AM, Acosta M, Rizkalla SW, Bornet F, David P, Letanoux M et al. A moderate switch from high to low glycaemic-index foods for 3 weeks improves the metabolic control of Type I (IDDM) diabetic subjects. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 1988; 1(2):139-143	None of our protocol outcomes reported
FROST 1994 Frost G, Wilding J, Beecham J. Dietary advice based on the glycaemic index improves dietary profile and metabolic control in type 2 diabetic patients. Diabet Med. 1994; 11:397-401	Wrong population: type 2 diabetes
FROST 1999 Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. Lancet. 1999; 353(9158):1045-1048	Wrong population: general population, not type 1 diabetes and no type 1 diabetes subgroup analysis
GARCIA-LOPEZ 2013 Garcia-Lopez JM, Gonzalez-Rodriguez M, Pazos-Couselo M, Gude F, Prieto-Tenreiro A, and Casanueva F. Should the amounts of fat and protein be taken into consideration to calculate the lunch prandial insulin bolus? Results from a randomized crossover trial. Diabetes Technol.Ther. 2013; 15 (2):166-171	Not GI diets: CHO counting method in test meals with same CHO content but different protein/fat content
GERARD 1981 Gerard J, Luyckx AS, Lefebvre PJ. Improvement of metabolic control in insulin dependent diabetics treated with the alpha-glucosidase inhibitor acarbose for two months. Diabetologia. 1981; 21(5):446-451	Does not answer the question: not GI diets but effects of acarbose during post-meal exercise

Reference	Reason for exclusion
GIACCO 2000 Giacco R, Giacco A, Parillo M, D'Episopo L, Rivellese AA, Riccardi G, Lasorella G. Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in Type 1 diabetic patients. Diabetes Care. 2000; 23(10):1461-1466.	The study's definition of low GI does not fall into the generally accepted range of low GI and so it is not a fair comparison with the other studies
GILBERTSON 2001 Gilbertson H, Brand-Miller J, Thornburn A, Evands S, Chondros P, Werther G. The effect of flexible low glycemic index dietary advice versus measure carbohydrate exchange diets on glycemic control in children with type 1 diabetes. Diabetes Care. 2001; 24:1137-1143	Non-adult population
JARVI 1999 Jarvi A, Karlstrom B, Granfeldt Y, Bjorck I, Asp N, Vessby B. Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. Diabetes Care. 1999; 22: 10-18	Wrong population: type 2 diabetes
JENKINS 1987 Jenkins DJ, Wolever TM, Collier GR, Ocana A, Rao AV, Buckley G et al. Metabolic effects of a low-glycemic-index diet. American Journal of Clinical Nutrition. 1987; 46(6):968-975	Wrong population: healthy
JENKINS 1988 Jenkins DJ, Wolever TM, Bukley G, Lam KY, Giudici S, Kalmusky J, Jenkins AL, Patten RL, Bird J, Wong GS et al. Low glycemic-index starchy foods in the diabetic diet. Am J Clin Nutr. 1988; 48: 248-254	Wrong population: type 2 diabetes
JENKINS 2008 Jenkins AL, Jenkins DJA, Wolever TMS, Rogovik AL, Jovanovski E, Bozikov V et al. Comparable postprandial glucose reductions with viscous fiber blend enriched biscuits in healthy subjects and patients with diabetes mellitus: acute randomized controlled clinical trial. Croatian Medical Journal. 2008; 49(6):772-782	Wrong population: healthy and type 2 diabetes
KHAW 2001 Khaw KT, Wareham N, Luben R, Bingham S, Oakes S, Welch A et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). BMJ (Clinical Research Ed). 2001; 322(7277):15-18	Does not give info on GI diets.
KOMINDR 2001 Komindr S, Ingsriswang S, Lerdvuthisopon N, Boontawee A. Effect of long-term intake of Asian food with different glycemic indices on diabetic control and protein conservation in type 2 diabetic patients. 2001; J Med Assoc Thai. 84:85-97. 2001	Wrong population: type 2 diabetes
LIESE 2007 Liese AD, Gilliard T, Schulz M, D'Agostino RB, Jr., Wolever TM. Carbohydrate nutrition, glycaemic load, and plasma lipids: the Insulin Resistance Atherosclerosis Study. European Heart Journal. 2007; 28(1):80-87	Wrong population: general population and no type 1 diabetes subgroup analysis

Reference	Reason for exclusion
LIVESEY 2008 Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health - A systematic review and meta-analysis: Relations between dietary glycemic properties and health outcomes. American Journal of Clinical Nutrition. 2008; 87(1):258S-268S	SR/MA – used as a source of references
LUSCOMBE 1999 Luscombe N, Noakes M, Clifton P. Diets high and low in glycaemic index versus high monounsaturated fat diets: effects on glucose and lipid metabolism in NIDDM. Eur J Clin Nutr. 1999; 53: 473-478	Wrong population: type 2 diabetes
OPPERMAN 2005 Opperman M, Venter CS, Oosthuizen W, Thompson RL. Some health benefits of low glycaemic index diets - A systematic review. South African Journal of Clinical Nutrition. 2005; 18(3):214-221	SR/MA – used as a source of references
PARILLO 2009 Parillo M, Rivellese AA, Annuzzi G, Bozzetto L, Alessandrini R, Riccardi G et al. Effects of meals with different glycemic index on postprandial blood glucose response in type 1 diabetic patients treated with CSII. Diabetes. 2009; 58	Conference abstract – now published (Parillo 2011) and has been included in this review
PETERSON 1986 Peterson DB, Lambert J, Gerring S, Darling P, Carter RD, Jelfs R et al. Sucrose in the diet of diabetic patients--just another carbohydrate? Diabetologia. 1986; 29(4):216-220	Not true GI diet – just partial replacement of some of the complex CHOs with sucrose
RABASA-LHORET 2001 Rabasa-Lhoret R, Burelle Y, Ducros F, Bourque J, Lavoie C, Massicotte D et al. Use of an alpha-glucosidase inhibitor to maintain glucose homoeostasis during postprandial exercise in intensively treated Type 1 diabetic subjects. Diabetic Medicine. 2001; 18(9):739-744	Does not answer the question: not GI diets but effects of acarbose
SAMANTA 1985 Samanta A, Burden AC, Jones GR. Plasma glucose responses to glucose, sucrose, and honey in patients with diabetes mellitus: An analysis of glycaemic and peak incremental indices. Diabetic Medicine. 1985; 2(5):371-373	Wrong outcomes: not those specified in our protocol. Very short follow-up – only 120 mins
SANTACROCE 1990 Santacroce G, Forlani G, Giangiulio S, Galuppi V, Pagani M, Vannini P. Long-term effects of eating sucrose on metabolic control of type 1 (insulin-dependent) diabetic outpatients. Acta Diabetologica Latina. 1990; 27(4):365-370	Not true GI diet – just partial replacement of some of the High GI food with sucrose
SLAMA 1981 Slama G, Klein JC, Delage A, Ardila E, Lemaignen H, Papoz L et al. Correlation between the nature and amount of carbohydrate in meal intake and insulin delivery by the artificial pancreas in 24 insulin-dependent diabetics. Diabetes. 1981; 30(2):101-105	Wrong outcomes; short follow-up (1 day); artificial pancreas study
SLAMA 1984 Slama G, Haardt MJ, Jean-Joseph P, Costagliola D, Goicolea I, Bornet F et al.	Wrong outcomes; short follow-up (180 mins); artificial pancreas study

Reference	Reason for exclusion
Sucrose taken during mixed meal has no additional hyperglycaemic action over isocaloric amounts of starch in well-controlled diabetics. Lancet. 1984; 2(8395):122-125	
SOUTO 2013 Souto DL, Zajdenverg L, Rodacki M, Rosado EL. Does sucrose intake affect antropometric variables, glycemia, lipemia and C-reactive protein in subjects with type 1 diabetes?: A controlled-trial. Diabetology and Metabolic Syndrome. 2013; 5(1)	Not true GI diet – just supplementation with sucrose
STANKO 1990 Stanko RT, Mitrakou A, Greenawalt K, Gerich J. Effect of dihydroxyacetone and pyruvate on plasma glucose concentration and turnover in noninsulin-dependent diabetes mellitus. Clinical Physiology and Biochemistry. 1990; 8(6):283-288	Wrong population: type 2 diabetes
SUBIAS 2011 Subias D, Perez-Gandia C, Hernando ME, Pons B, Garcia-Saez G, Martinez-Sarriegui I et al. First clinical experience using an on-line glucose prediction algorithm for interprandial optimisation in type 1 diabetes (DM1). Diabetes Technology and Therapeutics. 2011; 13(2):276	Conference abstract
THOMAS 2009 Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database of Systematic Reviews. 2009;(1):CD006296	Cochrane SR/MA – used as a source of references
THOMAS 2010 Thomas DE, Elliott EJ. The use of low-glycaemic index diets in diabetes control. British Journal of Nutrition. 2010; 104(6):797-802	SR/MA – used as a source of references
TOELLER 2001 Toeller M, Buyken AE, Heitkamp G, Cathelineau G, Ferriss B, Michel G. Nutrient intakes as predictors of body weight in European people with type 1 diabetes. International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity. 2001; 25(12):1815-1822	Wrong outcomes: not those specified in our protocol - looks at effects on weight
TORSDOTTIR 1986 Torsdottir I, Alpsten M, Andersson H. Effect of different starchy foods in composite meals on gastric emptying rate and glucose metabolism. II. Comparisons between potatoes, rice and white beans in diabetic subjects. Human Nutrition Clinical Nutrition. 1986; 40(5):397-400	Wrong outcomes; Wrong population (<70% type 1 diabetes and no type 1 diabetes subgroup analysis); Wrong follow-up: 1 day; wrong intervention –meals had different protein and CHO content, as well as testing the different sources of CHO used
URITA 2011 Urita Y, Sugimoto M, Noda T, Watanabe D, Iwashita S, Hamada K et al. Effects of soybean nutrition bar made from whole soy powder on postprandial blood glucose and lipids in patients with diabetes mellitus. Clinical Nutrition,	Conference abstract

Reference	Reason for exclusion
Supplement. 2011; 6(1):221	
WEST 2011 West DJ, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R et al. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. Journal of Sports Sciences. 2011; 29(3):279-289	Post-exercise specific diets – not general GI diets
WOLEVER 1985 Wolever TMS, Nuttall FQ, Lee R. Prediction of the relative blood glucose response of mixed meals using the white bread glycemic index. Diabetes Care. 1985; 8(5):418-428	Wrong outcomes. Data from other previously published studies
WOLEVER 1990 Wolever TM, Jenkins DJ, Vuksan V, Josse RG, Wong GS, Jenkins AL. Glycemic index of foods in individual subjects. Diabetes Care. 1990; 13(2):126-132	Wrong population: <70% type 1 diabetes and no type 1 diabetes subgroup analysis
WOLEVER 1992 Wolever T, Jenkins D, Vuksan V, Jenkins A, Wong G, Josse R. Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. Diabetes Care. 1992; 15:562-564	Wrong population: type 2 diabetes
WOLEVER 1992 Wolever T, Jenkins D, Vuksan V, Jenkins A, Buckley G, Wong G, Josse RG. Beneficial effect of a low glycaemic index diet in type 2 diabetes. Diabet Med. 1992; 9:451-458	Wrong population: type 2 diabetes
SCHMIDT 2014 S. Schmidt, B. Schelde, and K. Norgaard. Effects of advanced carbohydrate counting in patients with Type 1 diabetes: a systematic review. *Diabet Med* 31 (8):886-896, 2014.	SR – used as a source of references

K.3 Blood glucose monitoring

K.3.1 HbA1c

Reference	Reason for exclusion
Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. The Kroc Collaborative Study Group. New England Journal of Medicine. 1984; 311(6):365-372. (Guideline Ref ID ANON1984)	Not question of interest
Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. Diabetes Care. 1987; 10(1):1-19. (Guideline Ref ID ANON1987)	Not question of interest
Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research	Not question of interest

Reference	Reason for exclusion
Group. Annals of Internal Medicine. 1998; 128(7):517-523. (Guideline Ref ID ANON1998A)	
Ahmann AJ, Cheng P, Beck RW, Bergenstal RM, Bode BW, Garg SK et al. Factors associated with hemoglobin A1c levels among adult participants in the t1d exchange clinic registry. Diabetes. 2012; 61:A357. (Guideline Ref ID AHMANN2012)	Not question of interest
Akalin S, Berntorp K, Ceriello A, Das AK, Kilpatrick ES, Koblik T et al. Intensive glucose therapy and clinical implications of recent data: a consensus statement from the Global Task Force on Glycaemic Control. International Journal of Clinical Practice. 2009; 63(10):1421-1425. (Guideline Ref ID AKALIN2009)	Not question of interest, studies on type 2 diabetes mellitus populations
Aman J, Holmgren LG. Treatment with insulin Glargin or Detemir during 24 months from onset in children and adolescents with T1DM. Pediatric Diabetes. 2011; 12:123. (Guideline Ref ID AMAN2011)	Not question of interest
Anderson SG, Narayanan RP, Amlesh J, Qureshi MZ, Heald AH. Type 1 diabetes in Cheshire: cardiometabolic risk factor trends (2004-2009). Primary Care Diabetes. 2012; 6(2):123-126. (Guideline Ref ID ANDERSON2012)	Not question of interest
Bailey TS, Zisser HC, Garg SK. Reduction in hemoglobin A1C with real-time continuous glucose monitoring: results from a 12-week observational study. Diabetes Technology and Therapeutics. 2007; 9(3):203-210. (Guideline Ref ID BAILEY2007)	Not question of interest
Bangstad HJ, Osterby R, Dahl-Jørgensen K, Berg KJ, Hartmann A, Hanssen KF. Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. Diabetologia. 1994; 37(5):483-490. (Guideline Ref ID BANGSTAD1994)	Not question of interest, measure of glucose control was not HbA1c
Barrett T. Type 2 diabetes mellitus: Incidence, management andprognosis. Paediatrics and Child Health. 2013; 23(4):163-167. (Guideline Ref ID BARRETT2013)	Wrong population
Battelino T, Bolinder J. Clinical use of real-time continuous glucose monitoring. Current Diabetes Reviews. 2008; 4(3):218-222. (Guideline Ref ID BATTELINO2008)	Not question of interest
Battelino T, Bode BW. Continuous glucose monitoring in 2010. International Journal of Clinical Practice Supplement. 2011;(170):10-15. (Guideline Ref ID BATTELINO2011A)	Not question of interest
Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R et al. The SWITCH study: Continuous glucose monitoring in type 1 diabetes. Pediatric Diabetes. 2011; 12:30. (Guideline Ref ID BATTELINO2011B)	Not question of interest
Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial.	Not question of interest

Reference	Reason for exclusion
Diabetologia. 2012; 55(12):3155-3162. (Guideline Ref ID BATTELINO2012)	
Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011; 34(4):795-800. (Guideline Ref ID BATTELINO2011)	Not question of interest
Battelino T, Phillip M. Real-time continuous glucose monitoring in randomized control trials. Pediatric Endocrinology Reviews. 2010; 7 Suppl 3:401-404. (Guideline Ref ID BATTELINO2010)	Narrative
Beck R, Steffes M, Xing D, Ruedy K, Mauras N, Wilson DM et al. The interrelationships of glycemic control measures: HbA1c, glycated albumin, fructosamine, 1,5-anhydroglucitrol, and continuous glucose monitoring. Pediatric Diabetes. 2011; 12(8):690-695. (Guideline Ref ID BECK2011)	Narrative
Benhalima K, Standl E, Mathieu C. The importance of glycemic control: how low should we go with HbA1c? Start early, go safe, go low. Journal of Diabetes and Its Complications. 2011; 25(3):202-207. (Guideline Ref ID BENHALIMA2011)	Narrative
Bergenstal RM, Johnson M, Powers MA, Wynne A, Vlajnic A, Hollander P et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. Diabetes Care. 2008; 31(7):1305-1310. (Guideline Ref ID BERGENSTAL2008)	Wrong population
Billiard A, Rohmer V, Roques MA, Joseph MG, Suraniti S, Giraud P et al. Telematic transmission of computerized blood glucose profiles for IDDM patients. Diabetes Care. 1991; 14(2):130-134. (Guideline Ref ID BILLIARD1991)	Not question of interest
Bode B, Hirsch IB. Sustained reduction of biochemical, clinical and severe hypoglycaemia with extended CGM use: Results of JDRF CGM six month extension study. Diabetologia. 2009; 52(S1):S235. (Guideline Ref ID BODE2009)	Not question of interest
Buckingham BA, Tanner JP. Factors predictive of continuous glucose monitoring (CGM) use and benefit in the JDRF CGM RCT. Diabetes. 2009; 58. (Guideline Ref ID BUCKINGHAM2009)	Not question of interest
Cagliero E, Levina EV, Nathan DM. Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. Diabetes Care. 1999; 22(11):1785-1789. (Guideline Ref ID CAGLIERO1999)	Not question of interest intervention is a bench top analyser for HbA1c levels
Chetty VT, Almulla A, Odueyungbo A, Thabane L. The effect of continuous subcutaneous glucose monitoring (CGMS) versus intermittent whole blood finger-stick glucose monitoring (SBGM) on hemoglobin A1c (HbA1c) levels in Type I diabetic patients: a systematic review. Diabetes Research and Clinical Practice. 2008; 81(1):79-87. (Guideline Ref ID CHETTY2008)	Not question of interest
Colwell JA. The feasibility of intensive insulin management in non-insulin-	Wrong population

Reference	Reason for exclusion
dependent diabetes mellitus. Implications of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in NIDDM. Annals of Internal Medicine. 1996; 124(1 Pt 2):131-135. (Guideline Ref ID COLWELL1996)	
Currie CJ, Poole CD, Papo NL. An overview and commentary on retrospective, continuous glucose monitoring for the optimisation of care for people with diabetes. Current Medical Research and Opinion. 2009; 25(10):2389-2400. (Guideline Ref ID CURRIE2009)	Narrative
Dagogo-Jack S. Pitfalls in the use of HbA 1c as a diagnostic test: The ethnic conundrum. Nature Reviews Endocrinology. 2010; 6(10):589-593. (Guideline Ref ID DAGOGOJACK2010)	Not question of interest
Davidson JA. Coming to terms with the reality: Are international diabetes treatment guidelines attainable in clinical practice? Point. International Journal of Clinical Practice, Supplement. 2003;(138):3-8. (Guideline Ref ID DAVIDSON2003A)	Narrative
Davidson JA. Treatment of the patient with diabetes: importance of maintaining target HbA(1c) levels. Current Medical Research and Opinion. 2004; 20(12):1919-1927. (Guideline Ref ID DAVIDSON2004)	Narrative
Doyle EA, Weinzimer SA, Steffen AT, Ahern JA, Vincent M, Tamborlane WV. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. Diabetes Care. 2004; 27(7):1554-1558. (Guideline Ref ID DOYLE2004)	Not question of interest
Dreiher J, Ginsberg G, Rabinowitz G, Raskin-Segal A, Weitzman R, Porath A. Estimation of mortality savings due to a national program for diabetes care. European Journal of Internal Medicine. 2009; 20(3):307-312. (Guideline Ref ID DREIHER2009)	Not question of interest
Duran-Valdez E, Burge MR, Broderick P, Shey L, Valentine V, Schrader R et al. Insulin timing-a beneficial addition to intensive insulin therapy in type 1 diabetes. Diabetes. 2012; 61:A246. (Guideline Ref ID DURANVALDEZ2012A)	Not question of interest
Dzebisashvili T. HbA1c for diabetes mellitus diagnosis. Journal of Diabetes. 2011; 3:99. (Guideline Ref ID DZEBISASHVILI2011)	Narrative
Eby E, Gelwicks S, Marchlowska PA. HbA1c test utilization among hospitalized patients with hyperglycemia. Value in Health. 2012; 15(7):A534-A535. (Guideline Ref ID EBY2012)	Not question of interest
Edson EJ, Le TK, Nelson DR, Haldane D, Mendelsohn AB, Pillemer S et al. Macrovascular complications may be associated with tighter glycaemic control in patients with type 1 diabetes: An analysis of primary care data in the UK. Diabetologia. 2010; 53:S504. (Guideline Ref ID EDSON2010)	Abstract with insufficient information
Einhorn D, Handelsman Y, Bode BW, Endahl L, Mersebach H, King AB.	Not question of interest

Reference	Reason for exclusion
Subjects achieving good glycemic control (HbA1c <7.0%) experience a lower rate of confirmed and nocturnal confirmed hypoglycemia with insulin degludec than with insulin glargine: A meta-analysis of phase 3a trials. Endocrine Reviews. 2012; 33(3 MeetingAbstracts). (Guideline Ref ID EINHORN2012)	
el-Kebbi IM, Ziemer DC, Gallina DL, Phillips LS. Diabetes in urban African-Americans. VI. Utility of fasting or random glucose in identifying poor glycemic control. Diabetes Care. 1998; 21(4):501-505. (Guideline Ref ID ELKEBBI1998)	Not question of interest
Fall K, Garmo H, Gudbjornsdottir S, Stattin P, Zethelius B. Diabetes mellitus and prostate cancer risk; A nationwide case-control study within PCBaSe Sweden. Cancer Epidemiology Biomarkers and Prevention. 2013; 22(6):1102-1109. (Guideline Ref ID FALL2013)	Not question of interest
Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. Journal of Clinical Endocrinology and Metabolism. 2009; 94(3):729-740. (Guideline Ref ID FATOURECHI2009)	Not question of interest
Folsom L, Harris D, Mennito S, Bowlby D, Simpson K. Assessing adherence to american diabetic association recommendations for hemoglobin A1C goals. Journal of Investigative Medicine. 2012; 60(1):461. (Guideline Ref ID FOLSOM2012)	Not question of interest
Fujii H, Watanabe Y, Ueki A, Ohno A, Kato M, Kondo K et al. An increased dose of insulin detemir improves glycaemic control and reduces body weight of Japanese patients with diabetes. International Journal of Clinical Practice. 2010; 64(11):1512-1519. (Guideline Ref ID FUJII2010)	Not question of interest
Gao Y, Pan CY, Zou DJ, Xu ZR, Liu XM, Guo XH. [Postprandial glycemic control using insulin aspart with NPH in inadequately controlled diabetics]. Zhonghua Yi Xue Za Zhi. 2009; 89(28):1960-1963. (Guideline Ref ID GAO2009)	Not question of interest
Garg SK, Kelly WC, Freson BJ, Petrucci RE, Ritchie PJ. Treat-to-target technosphere insulin in patients with type 1 diabetes. Diabetes. 2011; 60:A257. (Guideline Ref ID GARG2011B)	Not question of interest
Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care. 2006; 29(1):44-50. (Guideline Ref ID GARG2006)	Not question of interest
Garg SK, Mathieu C, Rais N, Gao H, Tobian JA, Gates JR et al. Two-year efficacy and safety of AIR inhaled insulin in patients with type 1 diabetes: An open-label randomized controlled trial. Diabetes Technology and Therapeutics. 2009; 11 Suppl 2:S5-S16. (Guideline Ref ID GARG2009)	Not question of interest
Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ et al. Use of	Not question of interest

Reference	Reason for exclusion
continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: a prospective 6-month study. Diabetes Care. 2011; 34(3):574-579. (Guideline Ref ID GARG2011)	
Genuth S. Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endocrine Practice. 2006; 12 Suppl 1:34-41. (Guideline Ref ID GENUTH2006)	Narrative
Gerstl EM, Rabl W, Rosenbauer J, Grobe H, Hofer SE, Krause U et al. Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. European Journal of Pediatrics. 2008; 167(4):447-453. (Guideline Ref ID GERSTL2008)	Wrong population
Ginis Z, Ozturk G, Sirmali R, Yalcindag A, Dulgeroglu Y, Delibasi T et al. The role of HbA1c as a screening and diagnostic test for diabetes mellitus in Ankara. Turkish Journal of Medical Sciences. 2012; 42(SUPPL.2):1430-1436. (Guideline Ref ID GINIS2012)	Not question of interest
Giugliano D, Ceriello A, Esposito K. Glucose metabolism and hyperglycemia. American Journal of Clinical Nutrition. 2008; 87(1):217S-222S. (Guideline Ref ID GIUGLIANO2008)	Not question of interest
Golden SH, Sapir T. Methods for insulin delivery and glucose monitoring in diabetes: summary of a comparative effectiveness review. Journal of Managed Care Pharmacy. 2012; 18(6 Suppl):S1-17. (Guideline Ref ID GOLDEN2012)	Not question of interest
Gomes MB, Cobas R, Matheus A, Tannus L, Negrato C, Pedrsa H et al. Type 1 diabetes average glycemic control in the public health system of a developing country. The first nationwide survey in type 1 diabetes in Brazil. Diabetes. 2011; 60:A633. (Guideline Ref ID GOMES2011)	Not question of interest
Gottesman I, Girard M, Shorey S. A prospective registry to identify patients' characteristics associated with achieving target metabolic control after three months treatment with insulin glulisine in type 1 and 2 diabetes mellitus patients previously uncontrolled on basal insulin and/ or other anti-diabetic treatment (api registry). Value in Health. 2011; 14(7):A473-A474. (Guideline Ref ID GOTTESMAN2011)	Not question of interest
Govan L, Wu O, Briggs A, Colhoun HM, Fischbacher CM, Leese GP et al. Achieved levels of HbA1c and likelihood of hospital admission in people with type 1 diabetes in the Scottish population: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetes Care. 2011; 34(9):1992-1997. (Guideline Ref ID GOVAN2011)	Not outcome of interest, protocol does not include hospitalisation
Grossi SAA, Lottenberg SA, Lottenberg AM, Della Manna T, Kuperman H. Home blood glucose monitoring in type 1 diabetes mellitus. Revista Latino-	Not question of interest

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Americana De Enfermagem. 2009; 17(2):194-200. (Guideline Ref ID GROSSI2009)	
Heller S, Francisco AMO, Pei H, Russell-Jones D. Basal-bolus therapy with insulin degludec improves long-term glycaemic control with less nocturnal hypoglycaemia compared with insulin glargine in Type 1 diabetes: Results of a one year trial. Diabetic Medicine. 2012; 29:23-24. (Guideline Ref ID HELLER2012A)	Not question of interest
Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clinical Therapeutics. 2009; 31(10):2086-2097. (Guideline Ref ID HELLER2009)	Not question of interest
Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012; 379(9825):1489-1497. (Guideline Ref ID HELLER2012)	Not question of interest
Hermansen K, Heller S, Andersen M, Russell-Jones DL. Insulin detemir reduces hypoglycemic risk at comparable HbAlc values compared to NPH Insulin in patients with type 1 diabetes. Diabetes. 2009; 58. (Guideline Ref ID HERMANSEN2009)	Not question of interest
Hermansen K, Heller S, Andersen M, Russell-Jones DL. Lower rate of hypoglycaemia but comparable glycaemic control with insulin detemir compared to NPH insulin in patients with type l diabetes. Diabetologia. 2009; 52(S1):S359. (Guideline Ref ID HERMANSEN2009A)	Not question of interest
Higgins TN, Tran D, Cembrowski GS, Shalapay C, Steele P, Wiley C. Is HbA1c a good screening test for diabetes mellitus? Clinical Biochemistry. 2011; 44(17-18):1469-1472. (Guideline Ref ID HIGGINS2011)	Not question of interest
Hirsch IB, Meneghini LF, Landstedt-Hallin L, Rasmussen S, Lassota N, Vora J. Less nocturnal hypoglycemia for insulin degludec vs. insulin glargine in subjects with T1DM and baseline A1c of 7.5-8.5%: A meta-analysis. Diabetes. 2012; 61:A299-A300. (Guideline Ref ID HIRSCH2012)	Not question of interest
Home P, Haddad J, Latif ZA, Soewondo P, Benabbas Y, Litwak L et al. Comparison of National/Regional Diabetes Guidelines for the Management of Blood Glucose Control in non-Western Countries. Diabetes Therapy. 2013; 4(1):91-102. (Guideline Ref ID HOME2013)	Not question of interest
Howard C, Ren H, Rossiter A, Boss A. Reduced incidence and frequency of hypoglycaemia in an integrated analysis of pooled data from clinical trials of subjects with type 1 diabetes using prandial inhaled Technosphere insulin. Diabetologia. 2009; 52(S1):S386-S387. (Guideline Ref ID HOWARD2009A)	Not question of interest
Howard JA, Sommers R, Gould ON, Mancuso M. Effectiveness of an HbA1c tracking tool on primary care management of diabetes mellitus: glycaemic	Not question of interest

Reference	Reason for exclusion
control, clinical practice and usability. Informatics in Primary Care. 2009; 17(1):41-46. (Guideline Ref ID HOWARD2009)	
Hsu CC, Chang HY, Huang MC, Hwang SJ, Yang YC, Lee YS et al. HbA1c variability is associated with low-level (micro) albuminuria development in type 2 diabetes: a 7-year prospective cohort study. Diabetologia. 2012; 55(12):3163-3172. (Guideline Ref ID HSU2012)	Wrong population
Hutchinson MS, Joakimsen RM, Njolstad I, Schirmer H, Figenschau Y, Jorde R. Glycated hemoglobin in diagnosis of diabetes mellitus and pre-diabetes; validation by oral glucose tolerance test. The Tromso OGTT Study. Journal of Endocrinological Investigation. 2012; 35(9):835-840. (Guideline Ref ID HUTCHINSON2012)	Not question of interest
Jaacks LM, Bell RA, Dabelea D, D'Agostino RB, Dolan LM, Imperatore G et al. Diabetes self-management education patterns associated with glycemic control in youth with type 1 diabetes. Diabetes. 2012; 61:A20-A21. (Guideline Ref ID JAACKS2012)	Not question of interest
Kilpatrick ES, Rigby AS, Atkin SL. Variability in the relationship between mean plasma glucose and HbA1c: implications for the assessment of glycemic control. Clinical Chemistry. 2007; 53(5):897-901. (Guideline Ref ID KILPATRICK2007)	Not question of interest
Kirsh SR, Aron DC. Choosing targets for glycaemia, blood pressure and low-density lipoprotein cholesterol in elderly individuals with diabetes mellitus. Drugs and Aging. 2011; 28(12):945-960. (Guideline Ref ID KIRSH2011)	Narrative
Klingensmith G, Pihoker C, DuBose S. Longitudinal HbA1c values in children and young adults with type 1 diabetes over the last decade: Results from the U.S. T1D Exchange clinic registry. Hormone Research in Paediatrics. 2012; 78:61-62. (Guideline Ref ID KLINGENSMITH2012)	Wrong population
Kuenen JC, Borg R, Kuik DJ, Zheng H, Schoenfeld D, Diamant M et al. Does glucose variability influence the relationship between mean plasma glucose and HbA1c levels in type 1 and type 2 diabetic patients? Diabetes Care. 2011; 34(8):1843-1847. (Guideline Ref ID KUENEN2011)	Narrative
Laakso M, Cederberg H. Glucose control in diabetes: which target level to aim for? Journal of Internal Medicine. 2012; 272(1):1-12. (Guideline Ref ID LAAKSO2012)	Narrative
Laffel L, Cali A, Mathieu C. The TEENS study: Understanding glycemic control and quality of life in children, adolescents, and young adults with type 1 diabetes mellitus. Pediatric Diabetes. 2012; 13:162. (Guideline Ref ID LAFFEL2012)	Wrong population
Larsen ML. The clinical usefulness of glucated haemoglobin in diabetes care evaluated by use of a medical technology assessment strategy. Danish Medical Bulletin. 1997; 44(3):303-315. (Guideline Ref ID LARSEN1997)	Not question of interest

Reference	Reason for exclusion
Li Y, Li Q, Li Cj, Wang Cj, Zheng Ym, Issa M et al. Comparison of HbA1c in Chinese patients with type 1 or type 2 diabetes randomized to twice daily insulin lispro low mix 25 or twice daily human insulin mix 30/70. Chinese Medical Journal. 2009; 122(21):2540-2546. (Guideline Ref ID LI2009)	Not question of interest
Little RR, Rohlfing CL, Sacks DB, National Glycohemoglobin Standardization Program (NGSP) Steering Committee. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. Clinical Chemistry. 2011; 57(2):205-214. (Guideline Ref ID LITTLE2011)	Not question of interest
Luddeke HJ, Sreenan S, Aczel S, Maxeiner S, Yenigun M, Kozlovski P et al. PREDICTIVE- a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. Diabetes, Obesity and Metabolism. 2007; 9(3):428-434. (Guideline Ref ID LUDDEKE2007)	Study protocol
Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB et al. Evidence of a Strong Association Between Frequency of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. Diabetes Care. 2013; 36(7):2009-2014. (Guideline Ref ID MILLER2013)	Not question of interest
Nau DP, Kumar RN. The relationship of diabetes mellitus performance indicators with self-reported health and patient satisfaction. Disease Management and Health Outcomes. 2002; 10(11):707-713. (Guideline Ref ID NAU2002)	Not question of interest
Neuhold S, Resl M, Huelsmann M, Strunk G, Adlbrecht C, Rath C et al. Repeat measurements of glycated haemoglobin A(1c) and N-terminal pro-B-type natriuretic peptide: divergent behaviour in diabetes mellitus. European Journal of Clinical Investigation. 2011; 41(12):1292-1298. (Guideline Ref ID NEUHOLD2011)	Not question of interest
Penning-van Beest FJA, Wolffenbuttel BHR, Herings RMC. Haemoglobin A1c goal attainment in relation to dose in patients with diabetes mellitus taking metformin: a nested, case-control study. Clinical Drug Investigation. 2008; 28(8):487-493. (Guideline Ref ID PENNINGVANBEEST2008)	Not question of interest
Perez Mendez LF, Alvarez-Garcia E, Alvarez-Vazquez P, Hervas E, Casteras A, Fajar L et al. Long-term improvement of metabolic control without increased risk of hypoglycaemia by intensive insulin regimens in type 1 diabetes patients treated in a regular clinical setting. Experimental and Clinical Endocrinology and Diabetes. 2007; 115(3):182-186. (Guideline Ref ID PEREZMENDEZ2007)	Not question of interest
Prazny M, oupal J, krha J. Variability in comparison of HbA1c levels with self-monitored mean blood glucose levels in type 1 diabetic patients. Diabetes. 2011; 60:A588. (Guideline Ref ID PRAZNY2011)	Not question of interest
Ramachandran A, Patwardhan M, Asirvatham AJ, Moharana AK, Pathak A, Saikia M. Insulin detemir improves glycemic control with better tolerability	Not question of interest

Reference	Reason for exclusion
and no weight gain in patients with type 1 or type 2 diabetes: 26 week data from the Indian cohort of PREDICTIVE study. Diabetes. 2009; 58. (Guideline Ref ID RAMACHANDRAN2009)	
Ramirez SPB, McCullough KP, Thumma JR, Nelson RG, Morgenstern H, Gillespie BW et al. Hemoglobin A1c levels and mortality in the diabetic hemodialysis population: Findings from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Diabetes Care. 2012; 35(12):2527-2532. (Guideline Ref ID RAMIREZ2012)	Not question of interest
Ray KK, Kondapally Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009; 373(2):1765-1772. (Guideline Ref ID RAY2009)	Meta-analysis
Raz I, Linn T, Ziegler A-G, Schernthaner G, Bonnici F, Eren R et al. Recent data from DIA-AID 1, a global phase III clinical study using DiaPep277 for the treatment of newly diagnosed type 1 diabetes patients. Diabetologia. 2012; 55:S66. (Guideline Ref ID RAZ2012)	Not question of interest
Reichard P. Are there any glycemic thresholds for the serious microvascular diabetic complications? Journal of Diabetes and Its Complications. 1995; 9(1):25-30. (Guideline Ref ID REICHARD1995)	Narrative
Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care. 2002; 25(2):275-278. (Guideline Ref ID ROHLFING2002)	Narrative
Rudolf P, Bartelme A, Center for Insulin-Dependent Diabetes Access' Blue Ribbon Panel. A strategic action plan for achieving uncompromising "treat to target" in individuals with insulin-dependent diabetes: a report by the Center for Insulin-Dependent Diabetes Access' Blue Ribbon Panel. Diabetes Technology and Therapeutics. 2005; 7(5):755-767. (Guideline Ref ID RUDOLF2005)	Not question of interest
Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. Acta Diabetologica. 2013; 50(3):437-442. (Guideline Ref ID SARTORE2013)	Not question of interest
Sastre J, Pines PJ, Moreno J, Aguirre M, Blanco B, Calderon D et al. Metabolic control and treatment patterns in patients with type 1 diabetes in Castilla-La Mancha: the DIAbetes tipo 1 in Castilla La Mancha study. Endocrinologia y Nutricion. 2012; 59(9):539-546. (Guideline Ref ID SASTRE2012)	Non English publication
Saunders SA, Wallymahmed M, MacFarlane IA. Glycaemic control in a type 1 diabetes clinic for younger adults. QJM. 2004; 97(9):575-580. (Guideline Ref ID SAUNDERS2004)	Narrative
Schnell O, Eisfelder B, Standl E, Ziegler AG. High-dose intravenous insulin	Not question of interest

Reference	Reason for exclusion
infusion versus intensive insulin treatment in newly diagnosed IDDM. Diabetes. 1997; 46(10):1607-1611. (Guideline Ref ID SCHNELL1997)	
Schroeder EB, Hanratty R, Beaty BL, Bayliss EA, Havranek EP, Steiner JF. Simultaneous control of diabetes mellitus, hypertension, and hyperlipidemia in 2 health systems. Circulation Cardiovascular Quality and Outcomes. 2012; 5(5):645-653. (Guideline Ref ID SCHROEDER2012)	Not question of interest
Schweitzer M, Cavan DA, Ziegler R, Cranston I, Parkin C, Wagner RS. Is HbA1c a reliable measure for assessing glycaemic control? Diabetologia. 2012; 55:S404. (Guideline Ref ID SCHWEITZER2012)	Narrative
Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Annals of Internal Medicine. 2004; 141(6):421-431. (Guideline Ref ID SELVIN2004)	Meta-analysis; studies included in review
Sherr J, Tamborlane WV, Xing D, Tsalikian E, Mauras N, Buckingham B et al. Achievement of target A1C levels with negligible hypoglycemia and low glucose variability in youth with short-term type 1 diabetes and residual -cell function. Diabetes Care. 2012; 35(4):817-820. (Guideline Ref ID SHERR2012)	Wrong population
Shimazaki T, Kadowaki T, Ohyama Y, Ohe K, Kubota K. Hemoglobin A1c (HbA1c) predicts future drug treatment for diabetes mellitus: a follow-up study using routine clinical data in a Japanese university hospital. Translational Research. 2007; 149(4):196-204. (Guideline Ref ID SHIMAZAKI2007)	Not question of interest
Shogbon AO, Levy SB. Intensive glucose control in the management of diabetes mellitus and inpatient hyperglycemia. American Journal of Health-System Pharmacy. 2010; 67(10):798-805. (Guideline Ref ID SHOGBON2010)	Not question of interest
Singh BM, McNamara C, Wise PH. High variability of glycated hemoglobin concentrations in patients with IDDM followed over 9 years. What is the best index of long-term glycemic control? Diabetes Care. 1997; 20(3):306-308. (Guideline Ref ID SINGH1997)	Narrative
Stolker JM, Sun D, Conaway DG, Jones PG, Masoudi FA, Peterson PN et al. Importance of measuring glycosylated hemoglobin in patients with myocardial infarction and known diabetes mellitus. American Journal of Cardiology. 2010; 105(8):1090-1094. (Guideline Ref ID STOLKER2010)	Narrative
Sturm G, Lamina C, Zitt E, Lhotta K, Haider F, Neyer U et al. Association of HbA1c values with mortality and cardiovascular events in diabetic dialysis patients. the invor study and review of the literature. PloS One. 2011; 6(5). (Guideline Ref ID STURM2011)	Wrong population
Swift PGF, Skinner TC, de Beaufort CE, Cameron FJ, Aman J, Aanstoot HJ et al. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere childhood diabetes study group centre differences study 2005. Pediatric Diabetes. 2010; 11(4):271-278. (Guideline Ref ID SWIFT2010)	Wrong population

Reference	Reason for exclusion
Tamborlane WV, Ahern J. Implications and results of the Diabetes Control and Complications Trial. Pediatric Clinics of North America. 1997; 44(2):285-300. (Guideline Ref ID TAMBORLANE1997)	Narrative
Tamborlane WV, Ruedy KJ, Wysocki T, O'Grady M, Kollman C, Block J et al. JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: Research design and methods. Diabetes Technology and Therapeutics. 2008; 10(4):310-321. (Guideline Ref ID TAMBORLANE2008)	Not question of interest
Tan SMK, Shafiee Z, Wu LL, Rizal AM, Rey JM. Factors associated with control of type I diabetes in Malaysian adolescents and young adults. International Journal of Psychiatry in Medicine. 2005; 35(2):123-136. (Guideline Ref ID TAN2005)	Not question of interest
Tate H, Pillai A, Thomson G, Fernando DJ, Idris I. Responders to insulin therapy at 18 months among adults with newly diagnosed Type 1 diabetes: Which insulin regimen should we start? Diabetic Medicine. 2012; 29:174. (Guideline Ref ID TATE2012)	Narrative
Tavintharan S, Chew LS, Heng DM. A rational alternative for the diagnosis of diabetes mellitus in high risk individuals. Annals of the Academy of Medicine, Singapore. 2000; 29(2):213-218. (Guideline Ref ID TAVINTHARAN2000)	Not question of interest
Testa MA, Blonde L, Gill J, Turner RR, Simonson DC. Patient-centered outcomes and glycaemic variability in type 1 and type 2 diabetes: A cross-over trial of insulin glargine + glulisine vs premix analogue insulin. Diabetologia. 2010; 53:S395. (Guideline Ref ID TESTA2010)	Not question of interest
Thomas A, Heinemann L. Prediction of the risk to develop diabetes-related late complications by means of the glucose pentagon model: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring study. Journal of Diabetes Science and Technology. 2012; 6(3):572-580. (Guideline Ref ID THOMAS2012)	Not question of interest
Thomas A, Schonauer M, Achermann F, Schnell O, Hanefeld M, Ziegelasch HJ et al. The "glucose pentagon": assessing glycemic control of patients with diabetes mellitus by a model integrating different parameters from glucose profiles. Diabetes Technology and Therapeutics. 2009; 11(6):399-409. (Guideline Ref ID THOMAS2009)	Not question of interest
Tkac I. Effect of intensive glycemic control on cardiovascular outcomes and all-cause mortality in type 2 diabetes: Overview and metaanalysis of five trials. Diabetes Research and Clinical Practice. 2009; 86 Suppl 1:S57-S62. (Guideline Ref ID TKAC2009)	Wrong population
Tonella P, Fluck CE, Mullis PE. Metabolic control of type 1 diabetic patients followed at the University Children's Hospital in Berne: have we reached the goal? Swiss Medical Weekly. 2010; 140:w13057. (Guideline Ref ID TONELLA2010)	Narrative

Reference	Reason for exclusion
Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet. 2012; 379(9833):2252-2261. (Guideline Ref ID TRICCO2012)	Not question of interest
Tsui E, Barnie A, Ross S, Parkes R, Zinman B. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care . 2001; 24(10):1722-1727. (Guideline Ref ID TSUI2001)	Not question of interest
Turner R, Cull C, Holman R. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. Annals of Internal Medicine. 1996; 124(1 Pt 2):136-145. (Guideline Ref ID TURNER1996)	Wrong population
Twigg MJ, Bhattacharya D, Desborough JA, Wright DJ. Adherence to NICE guidance for prescribing in type 2 diabetes in primary care. International Journal of Pharmacy Practice. 2011; 19:43-44. (Guideline Ref ID TWIGG2011)	Wrong population
Ursic BN. CGM - Translating research trials to clinical practice. Pediatric Diabetes. 2009; 10:1. (Guideline Ref ID URSIC2009)	Narrative
Valle D, Santoro D, Bates P, Scarpa L, Italian Multicentre Lispro Study Group. Italian multicentre study of intensive therapy with insulin lispro in 1184 patients with Type 1 diabetes. Diabetes, Nutrition and Metabolism. 2001; 14(3):126-132. (Guideline Ref ID VALLE2001)	Not question of interest
Valle T, Koivisto VA, Reunanen A, Kangas T, Rissanen A. Glycemic control in patients with diabetes in Finland. Diabetes Care. 1999; 22(4):575-579. (Guideline Ref ID VALLE1999)	Not question of interest
Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews. 2008; Issue 3:CD006297. DOI:10.1002/14651858.CD006297.pub2. (Guideline Ref ID VARDI2008)	Not question of interest
Vijan S, Hofer TP, Hayward RA. Estimated benefits of glycemic control in microvascular complications in type 2 diabetes. Annals of Internal Medicine. 1997; 127(9):788-795. (Guideline Ref ID VIJAN1997)	Wrong population
Vora J, Meneghini LF, Landstedt-Hallin L, Rasmussen S, Lassota N, Hirsch IB. Subjects with Type 1 diabetes and baseline glycated haemoglobin of 7.5%-8.5% showed less nocturnal hypoglycaemia with insulin degludec compared with insulin glargine: A pooled analysis. Diabetic Medicine. 2013; 30:73. (Guideline Ref ID VORA2013)	Not question of interest
Vos FE, Schollum JB, Coulter CV, Manning PJ, Duffull SB, Walker RJ. Assessment of markers of glycaemic control in diabetic patients with chronic kidney disease using continuous glucose monitoring. Nephrology. 2012; 17(2):182-188. (Guideline Ref ID VOS2012)	Wrong population

Reference	Reason for exclusion
Williams ME, Lacson EJ, Teng M, Hakim RM, Lazarus JM. Extremes of glycemic control (HbA1c) increase hospitalization risk in diabetic hemodialysis patients in the USA. American Journal of Nephrology. 2009; 29(1):54-61. (Guideline Ref ID WILLIAMS2009)	Wrong population
Wilson DM, Xing D, Cheng J, Beck RW, Hirsch I, Kollman C et al. Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. Diabetes Care. 2011; 34(6):1315-1317. (Guideline Ref ID WILSON2011)	Wrong population
Wojciechowski P, Rys P, Lipowska A, Gaweska M, Malecki MT. Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnetrznej. 2011; 121(10):333-343. (Guideline Ref ID WOJCIECHOWSKI2011)	Not question of interest
Woo V, Clendenan J. Association of frequency of Self-Monitoring of Blood Glucose (SMBG) and HbA1c in the clinical practice. Diabetes. 2011; 60:A241. (Guideline Ref ID WOO2011)	Not question of interest
Xing D, Kollman C, Beck RW, Tamborlane WV, Laffel L, Buckingham BA et al. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technology and Therapeutics. 2011; 13(3):351-358. (Guideline Ref ID XING2011)	Not question of interest
Yamamoto-Honda R, Kitazato H, Hashimoto S, Takahashi Y, Yoshida Y, Hasegawa C et al. Distribution of blood glucose and the correlation between blood glucose and hemoglobin A1c levels in diabetic outpatients. Endocrine Journal. 2008; 55(5):913-923. (Guideline Ref ID YAMAMOTOHONDA2008)	Not question of interest
Young B, Henderson J, Turner B, Hillson R. The English national diabetes audit 2003-2008. Diabetologia. 2009; 52(S1):S101. (Guideline Ref ID YOUNG2009)	Not question of interest
Zhang L, Krzentowski G, Albert A, Lefebvre PJ. Factors predictive of nephropathy in DCCT Type 1 diabetic patients with good or poor metabolic control. Diabetic Medicine. 2003; 20(7):580-585. (Guideline Ref ID ZHANG2003)	Duplicate publication of study included in review
LACHIN 2014 JM. Lachin, Trevor J. Orchard, David M. Nathan, and DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. *Diabetes Care* 37 (1):39-43, 2014.	30 years DCCT. But data already reported in NATHAN 2005 study (which has already been included in our original review). 21% lower risk of CVD per 10% lower mean HbA1c.
KALTER 1991 O. Kalter-Leibovici, D. J. Van Dyk, L. Leibovici, N. Loya, A. Erman, I. Kremer, G.	Mixed population of young people and adults. No age

Reference	Reason for exclusion
Boner, J. B. Rosenfeld, M. Karp, and Z. Laron. Risk factors for development of diabetic nephropathy and retinopathy in Jewish IDDM patients. *Diabetes* 40 (2):204-210, 1991.	subgroup analysis and unclear % of adults.
WADEN 2009 J Waden, Carol Forsblom, Lena M. Thorn, Daniel Gordin, Markku Saraheimo, Per Henrik Groop, and Finnish Diabetic Nephropathy Study Group. A1C variability predicts incident cardiovascular events, low-level (micro) albuminuria, and overt diabetic nephropathy in patients with type 1 diabetes. *Diabetes* 58 (11):2649-2655, 2009.	Mixed population of young people and adults. No age subgroup analysis and unclear % of adults.
MACLEOD 1993 K. M. MacLeod, D. A. Hepburn, and B. M. Frier. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. *Diabet.Med.* 10 (3):238-245, 1993.	Mixed population of young people and adults. No age subgroup analysis and unclear % of adults.
SCHOENAKER 2014 D. A. J. M. Schoenaker, D. Simon, N. Chaturvedi, J. H. Fuller, and S. S. Soedamah-Muthu. Glycemic control and all-cause mortality risk in type 1 diabetes patients: The EURODIAB prospective complications study. *J.Clin.Endocrinol.Metab.* 99 (3):800-807, 2014.	Mixed population of young people and adults. No age subgroup analysis and unclear % of adults.
MOSKALET 1994 E. Moskalets, G. Galstyan, E. Starostina, M. Antsiferov, and E. Chantelau. Association of blindness to intensification of glycemic control in insulin-dependent diabetes mellitus. *J.Diabetes Complications* 8 (1):45-50, 1994.	Treatment study – shows effects of HbA1c after intensive glycaemic control on outcomes such as retinopathy
NATHAN 2014 Nathan DM, DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014; 37(1):9-16	Overview of 30 year DCCT/EDIC data. Alrady got the data included in more detailed publications (Aiello 2014; Lachin 2014; Martin 2014)
ARAKI 1993 A. Araki, H. Ito, A. Hattori, J. Inoue, T. Sato, M. Shiraki, and H. Orimo. Risk factors for development of retinopathy in elderly Japanese patients with diabetes mellitus. *Diabetes Care* 16 (8):1184-1186, 1993.	Wrong population: type 2 diabetes
BERLIN 2005 I. Berlin, C. I. Sachon, and A. Grimaldi. Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. *Diabetes Metab.* 31 (3 Pt 1):246-251, 2005.	Wrong outcomes: Hba1c by impaired hypo awareness, not by our pre-specified outcomes
COOPER 2013 MN. Cooper, Susan M. O'Connell, Elizabeth A. Davis, and Timothy W. Jones. A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia* 56 (10):2164-2170, 2013.	Wrong population: children and young people
DAVIS 1998 M. D. Davis, M. R. Fisher, R. E. Gangnon, F. Barton, L. M. Aiello, E. Y. Chew, F.	Wrong population: mix of type 1 diabetes and type 2

Reference	Reason for exclusion
L. Ferris, and G. L. Knatterud. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. *Invest Ophthalmol Vis Sci* 39 (2):233-252, 1998.	diabetes, <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
DIEDRICHS 2009 H. Diedrichs, R. Pfister, Z. Clement, J. Hagemeister, and C. A. Schneider. Delta-glycated hemoglobin: a novel independent risk factor for cardiovascular events in patients without diabetes mellitus. *J.Endocrinol.Invest.* 32 (7):564-567, 2009.	Wrong population: mix of type 1 diabetes and type 2 diabetes, <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
GENUTH 2013 SM. Genuth, Jye Yu Backlund, Margaret Bayless, David A. Bluemke, Patricia A. Cleary, Jill Crandall, John M. Lachin, Joao A. C. Lima, Culian Miao, Evrim B. Turkbey, and DCCT/EDIC Research Group. Effects of prior intensive versus conventional therapy and history of glycemia on cardiac function in type 1 diabetes in the DCCT/EDIC. *Diabetes* 62 (10):3561-3569, 2013.	Wrong outcome measures: not those pre-specified in our protocol.
GUNNLAUGSDOTTIR 2012 E. Gunnlaugsdottir, S. Halldorsdottir, R. Klein, G. Eiriksdottir, B. E. Klein, R. Benediktsson, T. B. Harris, L. J. Launer, T. Aspelund, V. Gudnason, M. F. Cotch, and F. Jonasson. Retinopathy in old persons with and without diabetes mellitus: the Age, Gene/Environment Susceptibility--Reykjavik Study (AGES-R). *Diabetologia* 55 (3):671-680, 2012.	Wrong population: mix of type 1 diabetes and type 2 diabetes, % type 1 diabetes not given, and no type 1 diabetes subgroup analysis.
KHAW 2001 K. T. Khaw, N. Wareham, R. Luben, S. Bingham, S. Oakes, A. Welch, and N. Day. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of european prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ (Clinical research ed.)* 322 (7277):15-18, 2001.	Wrong population: healthy and diabetes, but type of diabetes not mentioned.
KILPATRICK 2012 E. S. Kilpatrick. The rise and fall of HbA(1c) as a risk marker for diabetes complications. *Diabetologia* 55 (8):2089-2091, 2012.	Review – used as source of references.
MOSS 1988 S. E. Moss, R. Klein, and B. E. Klein. The incidence of vision loss in a diabetic population. *Ophthalmology* 95 (10):1340-1348, 1988.	Wrong population: mix of type 1 diabetes and type 2 diabetes, % type 1 diabetes not given, and no type 1 diabetes subgroup analysis.
OLSEN 1999 B. S. Olsen, J. Johannesen, A. K. Sjolie, K. Borch-Johnsen, P. Hougarrdss, B. Thorsteinsson, S. Prammingss, K. Marinelli, and H. B. Mortensen. Metabolic control and prevalence of microvascular complications in young Danish patients with Type 1 diabetes mellitus. Danish Study Group of Diabetes in Childhood. *Diabet.Med.* 16 (1):79-85, 1999.	Wrong population: young people and adults; % of adults not given and no adults subgroup analysis.
OSKARSON 1999 P. Oskarsson, U. Adamson, Sjobom N. Clausen, and P. E. Lins. Long-term follow-up of insulin-dependent diabetes mellitus patients with recurrent episodes of severe hypoglycaemia. *Diabetes Res.Clin.Pract.* 44 (3):165-174, 1999.	Unclear population: just says 'insulin treated' diabetes

Reference	Reason for exclusion
SINGH 2013 A Singh, Robert Donnino, Howard Weintraub, and Arthur Schwartzbard. Effect of strict glycemic control in patients with diabetes mellitus on frequency of macrovascular events. *Am.J.Cardiol.* 112 (7):1033-1038, 2013.	Review – used as source of references. Got all relevant refs already.
TAMBA 2013 S. M. Tamba, M. E. Ewane, A. Bonny, C. N. Muisi, E. Nana, A. Ellong, C. E. Mvogo, and S. H. Mandengue. Micro and macrovascular complications of diabetes mellitus in cameroon: Risk factors and effect of diabetic check-up - a monocentric observational study. *Pan Afr.Med.J.* 15, 2013.	Wrong population: mix of type 1 diabetes and type 2 diabetes, <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
WINKLEY 2007 K Winkley, Daniel Stahl, Trudie Chalder, Michael E. Edmonds, and Khalida Ismail. Risk factors associated with adverse outcomes in a population-based prospective cohort study of people with their first diabetic foot ulcer. *J.Diabetes Complications* 21 (6):341-349, 2007.	Wrong population: mix of type 1 diabetes and type 2 diabetes, <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
ZANDER 1997 E. Zander, P. Heinke, S. Herfurth, J. Reindel, F. E. Ostermann, and W. Kerner. Relations between diabetic retinopathy and cardiovascular neuropathy--a cross-sectional study in IDDM and NIDDM patients. *Exp.Clin.Endocrinol.Diabetes* 105 (6):319-326, 1997.	Results given only for univariate analysis – not taken into account confounders.
DECKERS 2001 S. Deckers, M. P. Hermans, and M. Buysschaert. Therapy, glycaemic control and complications in type 1 diabetic patients: results from a single centre cohort of 465 subjects. *Acta Clin Belg* 56 (5):289-296, 2001.	Article unavailable.
FULLERTON 2014 B Fullerton, Klaus Jeitler, Mirjam Seitz, Karl Horvath, Andrea Berghold, and Andrea Siebenhofer. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2:CD009122, 2014.	Blood glucose targets, not HbA1c.
BORG 2011 Borg R, Kuenen JC, Carstensen B, Zheng H, Nathan DM, Heine RJ et al. HbA1(c) and mean blood glucose show stronger associations with cardiovascular disease risk factors than do postprandial glycaemia or glucose variability in persons with diabetes: the A1C-Derived Average Glucose (ADAG) study. Diabetologia. 2011; 54(1):69-72.	Mixed population of type 1 diabetes and type 2 diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
BRINCHMANN 1992 Brinchmann-Hansen O, Dahl-Jorgensen K, Sandvik L, Hanssen KF. Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study. BMJ. 1992; 304(6818):19-22	Already ordered for original review and was an included study.
MINDER 2013 Minder AE, Albrecht D, Schafer J, Zulewski H. Frequency of blood glucose testing in well educated patients with diabetes mellitus type 1: How often is enough? Diabetes Research and Clinical Practice. 2013; 101(1):57-61	Does not answer the question: looks at number of SMBG mmts and effect on HbA1c.

Reference	Reason for exclusion
NATHAN 2005 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine. 2005; 353(25):2643-2653	DCCT (CV outcomes): Study already included in original review.
KONDURACKA 2013 E Konduracka, Grazyna Cieslik, Danuta Galicka-Latala, Pawel Rostoff, Artur Pietrucha, Pawel Latacz, Grzegorz Gajos, Maciej T. Malecki, and Jadwiga Nessler. Myocardial dysfunction and chronic heart failure in patients with long-lasting type 1 diabetes: a 7-year prospective cohort study. *Acta Diabetol.* 50 (4):597-606, 2013.	Wrong outcome: heart failure. Just shows generally HbA1c at baseline is a predictor of heart failure 7 years later.
RAY 2009 Ray KK, Kondapally Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009; 373(2):1765-1772	Already ordered for original review and was an included study. SR/MA.
SERVICE 2001 Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. Diabetologia. 2001; 44(10):1215-1220	SMBG targets, not HbA1c.
WORTH 1982A Worth R, Home PD, Johnston DG, Anderson J, Ashworth L, Burrin JM et al. Intensive attention improves glycaemic control in insulin-dependent diabetes without further advantage from home blood glucose monitoring: results of a controlled trial. BMJ. 1982; 285(6350):1233-1240	Does not answer question: RCT of monitoring urine glucose vs. blood glucose.
SPALLONE 1997 V. Spallone, M. R. Maiello, E. Cicconetti, and G. Menzinger. Autonomic neuropathy and cardiovascular risk factors in insulin-dependent and non insulin-dependent diabetes. *Diabetes Res.Clin.Pract.* 34 (3):169-179, 1997.	Wrong outcomes: neuropathy tests and CV tests – not actual clinical events.
ALLAN 2014 K. Allan, C. Garrett, S. Thomas, S. A. Amiel, and D. Hopkins. Factors contributing to mortality in Type 1 diabetes: A case control study. *Diabet Med* 31:115-116, 2014.	Conference abstract
ANDERSON 2014 B. J. Anderson, L. M. Laffel, C. Domenger, Dain M. Paule, V. Pilorget, C. Candelas, T. Danne, M. Phillip, C. Mazza, R. Hanas, S. Waldron, R. W. Beck, and C. Mathieu. Diabetes-specific health-related quality of life (QOL) in a sample of U.S. youth with type 1 diabetes (T1D) in the teens study. *Diabetes* 63:A325, 2014.	Conference abstract
BULUM 2014 T. Bulum, I. Prkacin, K. Blaslov, K. Zibar, and L. Duvnjak. Clinical and metabolic predictors of nonproliferative and proliferative/laser treated retinopathy in normoalbuminuric type 1 diabetic patients with normalor mildly impaired renal function. *Nephrol.Dial.Transplant.* 29:iii426-iii427, 2014.	Conference abstract

Reference	Reason for exclusion
CHAO 2014 J. H. Chao, A. Sussman, and I. B. Hirsch. Is sensible use of glycated albumin realistic in patients with diabetes mellitus-the sugar study. *J.Investig.Med.* 62 (1):204-205, 2014.	Conference abstract
COOPER 2014 M. N. Cooper, M. I. De Bock, T. W. Jones, and E. A. Davis. Predictors for vascular disease hospitalisations in young adults with childhood onset T1DM: Insights from 20 years of follow-up. *Diabetes* 63:A410-A411, 2014.	Conference abstract
DORCHY 2013 H. Dorchy, Arabi H. El, C. Melot, and D. Willems. A mathematical model to predict HbA1c levels from mean blood glucose in young type 1 diabetic patients. *Pediatr.Diabetes* 14:85-86, 2013.	Conference abstract
GARG 2014 S. Garg, B. W. Bode, R. Bergenstal, D. C. Klonoff, M. Mao, R. Weiss, and J. B. Welsh. Characteristics and predictors of nocturnal hypoglycemia in the run-in phase of the aspire in-home study. *Diabetes* 63:A242, 2014.	Conference abstract
GEORGE 2014 K. George, N. M. Patel, S. Mawri, B. Hachey, A. Michaels, D. Willens, and R. Parekh. What risk factors in patients with new onset diabetes mellitus increase the likelihood of developing pancreatic cancer? *Gastroenterology* 146 (5 SUPPL. 1):S-276, 2014.	Conference abstract
HERNANDEZ 2014 R. M. S. Hernandez, Y. L. Plasencia, D. A. Martel, J. R. Cordero, A. J. Ortega, A. C. Dominguez, F. J. N. Mogollan, and A. M. Wag ner. Preliminary evaluation of the ANAIS education programme for type 1 diabetes (T1D): A randomised controlled trial. *Diabetes* 63:A172, 2014.	Conference abstract
HOLMAN 2013 N. Holman and B. Young. Short term mortality in people with diabetes: Results from the national diabetes audit in England and Wales. *Diabetologia* 56:S186, 2013.	Conference abstract
JAISWAL 2014A M. Jaiswal, J. Divers, S. Isom, E. M. Urbina, L. M. Dolan, D. Dabelea, G. Imperatore, R. A. Bell, A. D. Liese, D. J. Pettitt, S. M. Marcovina, C. L. Martin, E. L. Feldman, and R. Pop-Busui. Prevalence and risk factors of cardiovascular autonomic neuropathy among youth with type 1 diabetes: Search cohort study. *Diabetes* 63:A145-A146, 2014.	Conference abstract
JAISWAL 2014 M. Jaiswal, J. Divers, S. Isom, C. L. Martin, A. D. Liese, L. M. Dolan, D. Dabelea, D. J. Pettitt, C. Pihoker, S. M. Marcovina, S. H. Saydah, B. Linder, R. A. Bell, R. Pop-Busui, and E. L. Feldman. Prevalence and clinical correlates of diabetic peripheral neuropathy among youth with type 1 diabetes: Search for diabetes in youth cohort study. *Diabetes* 63:A148-A149, 2014.	Conference abstract

Reference	Reason for exclusion
KALDARA 2014 E. Kaldara, E. Nana, C. Kapelios, E. Repasos, C. Pantsios, Z. Margari, N. Tentolouris, and J. Nanas. Intensive glycemic control in patients with diabetes mellitus and chronic heart failure appears to be associated with increased risk of hospitalization for heart failure deterioration. *Eur.J.Heart Fail.* 16:167, 2014.	Conference abstract
LEELARATHNA 2013C L. Leelarathna, S. A. Little, E. Walkinshaw, H. K. Tan, K. Kumareswaran, Solomon A. Lubina, D. Flanagan, S. Heller, J. A. M. Shaw, M. L. Evans, and E. Chow. Patients with longstanding type 1 diabetes show improved self awareness of hypoglycaemia measured during clamped hypoglycaemic challenges after a six month intensive treatment period in the HypoCOMPASS Study: Comparison of optimised multiple daily injections (MDI) and continuous insulin infusion therapy (CSII) with or without adjunctive real-time continuous glucose monitoring (RTCGM). *Diabet Med* 30:14, 2013.	Ordered for AWARE question. Was excluded as conference abstract.
MANNUCCI 2014 E. Mannucci, M. Monami, I. Dicembrini, A. Piselli, and M. Porta. Achieving HbA1c targets in clinical trials and in the real world: A systematic review and meta-analysis. *J.Endocrinol.Invest.* 37 (5):477-495, 2014.	SR/ MA – used as source of references. Does not answer the question and wrong outcomes: gives % of people reaching target HbA1c, but does not link HbA1c level to clinical outcomes. Meta-analysis contains studies using mixed population of diabetes with no type 1 diabetes subgroup analysis and <70% type 1 diabetes.
MCQUEEN 2014 R. Brett McQueen, Samuel L. Ellis, David M. Maahs, Heather D. Anderson, Kavita V. Nair, Anne M. Libby, and Jonathan D. Campbell. Association between glycated hemoglobin and health utility for type 1 diabetes. *Patient* 7 (2):197-205, 2014.	Wrong outcomes – Hec.
NAUGHTON 2014 MJ. Naughton, JP. Yi-Frazier, TM. Morgan, M Seid, JM. Lawrence, GJ. Klingensmith, B Waitzfelder, DA. Standiford, B Loots, and SEARCH for Diabetes in Youth Study Group. Longitudinal associations between sex, diabetes self-care, and health-related quality of life among youth with type 1 or type 2 diabetes mellitus. *J.Pediatr.* 164 (6):1376-1383, 2014.	Does not give results for HbA1c and QoL link in the type 1 diabetes adult subgroup
NITTALA 2014 M. G. Nittala, P. A. Keane, K. Zhang, and S. R. Sadda. Risk factors for proliferative diabetic retinopathy in a Latino American population. *Retina* 34 (8):1594-1599, 2014.	Wromng population: mixed diabetes with <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
NUNLEY 2014 K. Nunley, J. Saxton, T. J. Orchard, R. Jennings, H. Aizenstein, C. Ryan, J. C.	Conference abstract

Reference	Reason for exclusion
Zgibor, T. Costacou, R. Boudreau, R. G. Miller, and C. Rosano. Clinically significant cognitive dysfunction in middle-aged adults with childhood-onset type 1 diabetes: Prevalence and contributing factors. *Diabetes* 63:A89, 2014.	
PETROVSKI 2013 G. Petrovski, T. Milenkovic, B. Jovanovska, I. Ahmeti, and I. Bitovska. Intermittent glucose monitoring in type 1 diabetics on insulin pump: Is there difference in glycaemic control between real-time and retrospective analysis? *Diabetologia* 56:S442, 2013.	Conference abstract
RATHSMAN 2013 B. Rathsman, M. Donner, C. Ursing, and T. Nystrom. Long-term effects of intensive treatment in type 1 diabetes on all-cause mortality, cardiovascular mortality, and morbidity in cardiovascular disease: A long-term follow-up study. *Pediatr.Diabetes* 14:24, 2013.	Conference abstract
STADLER 2013 M. Stadler, S. Peric, H. Strohner-Kaestenbauer, R. Kramar, K. Irsigler, T. Kaestenbauer, F. Kronenberg, and R. Prager. Mortality and requirement of renal replacement therapy in people with type 1 diabetes: A 30 years prospective observational study. *Diabetologia* 56:S477-S478, 2013.	Conference abstract
SURKOVA 2013 E. V. Surkova, O. G. Motovilin, A. Y. Mayorov, and J. A. Shishkova. Glycaemic control and quality of life: Is there any relationship in young patients with type 1 diabetes? *Diabetologia* 56:S428, 2013.	Conference abstract
TESTA 2014 M. A. Testa, J. K. Gill, M. Su, L. Traylor, and D. C. Simonson. CGM and SMBG analytics predict hypoglycemic risk and symptoms during intensive insulin titration. *Diabetes* 63:A214, 2014.	Conference abstract
THOMAS 2012 A Thomas and L Heinemann. Prediction of the risk to develop diabetes-related late complications by means of the glucose pentagon model: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring study. *J Diabetes Sci Technol* 6 (3):572-580, 2012.	Already retrieved in pre-rerun evidence and excluded as did not answer the question. JDRF is also type 2 diabetes.
THOMAS 2013 S. Thomas, L. Yassa, D. Simpson, T. Evans, S. Amiel, A. Simonds, and D. Hopkins. Age, glycaemic control and social deprivation independently predict 10-year mortality in a UK type 1 diabetes cohort. *Diabetologia* 56:S136, 2013.	Conference abstract
VAN 2013 DE. Van, F. Barkhof, M. Klein, F. J. Snoek, R. G. Ijzerman, and M. Diamant. Selective cognitive decline is related to focal brain volume loss in type 1 diabetes patients with microangiopathy: A 4 year follow-up. *Diabetologia* 56:S524, 2013.	Conference abstract
VERDOIA 2014 M Verdoia, A Schaffer, E Cassetti, L Barbieri, MV Di Ruocco, P Perrone-Filardi,	Wrong population: not type 1 diabetes.

Reference	Reason for exclusion
P Marino, G De Luca, and Novara Atherosclerosis Study Group (. Glycosylated hemoglobin and coronary artery disease in patients without diabetes mellitus. *Am.J.Prev.Med.* 47 (1):9-16, 2014.	
YAN 2014 J. Yan, Y. Zhang, W. Xu, D. Yang, H. Deng, H. Ai, L. Liu, B. Yao, and J. Weng. Insulin injection regimens and glycemic control in guangdong type 1 diabetic patients. *Diabetes* 63:A644, 2014.	Conference abstract
ZHANG 2014 Y. Zhang, J. Yan, H. Deng, D. Yang, L. Liu, X. Zheng, S. Lin, B. Yao, and J. Weng. Factors associated with glycemic control in adults with type 1 diabetes used insulin pump. *Diabetes* 63:A603, 2014.	Conference abstract

K.3.2 SMBG targets, timing and frequency

Reference	Reason for exclusion
ABDELMOHSIN 2012 [20]	Wrong population: children. Wrong outcomes and predictor variables.
AHMANN 2012 [24]	Conference abstract. Got enough data already. See if now published.
AHRING 1992 [26]	Does not answer our question: new technology for SMBG. Will be included as part of the SMBG technologies question.
ALEXANDER 2000[28]	Wrong population: diabetes mellitus but does not mention how many are type 1 diabetes.
ALLEN 2001A [29]	Mixed population: adults and children. But most are children . Has an age 25 years+ subgroup analysis bt this is not for out question of interest.
ANDERSON 1970 [37]	Type 2 diabetic patients
ANDERSEN 1979 [36]	Conference abstract. SMBG effect on measures of retinopathy. See if now published.
ANDERSON 2012A[38]	Does not look at the link between SMBG and HbA1c or other outcomes
ANON 1986[1]	Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes. Will be used for

Reference	Reason for exclusion
	HbA1c question.
ANON 1986A [2]	Methods paper for DCCT
ANON 1995A[4]	No measure of SBMG.
ANON 1996[5]	Used original trial data (DCCT)
ANON 1998[7]	Wrong outcomes: autonomic nervous system function
ANON 2000A [10]	Follow-up to trial. Used original trial data.
ANON 2002B[13]	NHS national prescribing centre bulletin
ANON 2002D [12]	Not a relevant comparison. Associated HbA1c with microvascular complications
ANON 2003C[14]	Overview of DCCT and EDIC
ANON 2003D[15]	Newsletter about the DCCT trial
ANON 2007[17]	Review. Used as source of references.
ARFKEN 1998 [40]	Mixed population: adults and children; % of adults not known. Also wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes.
AVIGNON 1997[43]	Type 2 diabetic patients
BAILON 2009 [46]	Wrong population: hypo patients OR diabetes. Does not give % of each or how many were type 1 diabetes.
BERGENSTAL 2005 [52]	Details of a report but not the actual report!
BERGENSTAL 2012 [51]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (57%).
BHATTA 2002[53]	Clinical practice scenario.
BHORASKAR 2011[54]	Review on inpatient management.
BLEICHER 1980 [56]	Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes. This will be used

Reference	Reason for exclusion
	for the HbA1c question.
BLONDE 2012 [57]	Review. Used as source of references.
BODE 2010A [59]	Conference abstract. Main study results now published and have been ordered (BERGENSTAL 2012).
BODE2008A [58]	Review. Used as a source of references.
BORG 2010A [62]	Conference abstract. Looks at CGM not SMBG.
BREUER 2000 [65]	Review. Used as source of references. All type 2 diabetes and other populations.
BRINCHMANN 1992[67]	OSLO STUDY: 7 year results. Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes. Will be used for HbA1c question.
BROWNLEE 2006[68]	Editorial
CERIELLO 2008[80]	Review. Used as source of references.
CHASE 1989[83]	No investigation into SMBG
CHBAT 2005 [86]	Review. Used as a source of references.
CHELLIAH 2004[87]	Review. Used as a source of references.
CHENG 2009[88]	Review. Used as a source of references.
CLEARY 2006 [91]	Wrong outcomes: atherosclerosis/coronary artery calcification.
COLHOUN 2012[92]	Conference abstract. Does not look at SMBG.
COSTER 2000 [98]	HTA – used as source of references. Only 1 study found looking at frequency of SMBG in type 1 diabetes (RCT, Gordon 1991). We already have included this study in our review.
COX 1980 [99]	Wrong population: mixed population of adults and young people, but % adults not given.
CROFFORD 1987[101]	Not a relevant comparison. Compares different insulin regimens

Reference	Reason for exclusion
CROFFORD 1990[100]	DCCT interim results
CUGNET-ANCEAU 2009 [102]	Review. Used as a source of references.
DACOSTA 2010 [109]	Conference abstract. Wrong outcomes: endothelial-dependent response.
DAENEN 2010 [110]	Does not answer our question: CGM measurements not SMBG. But shows best times to monitor blood glucose.
DAHL 2010[111]	Summary of a conference talk.
DAHLJORGENSEN 1985 [112]	Not a relevant comparison.
DAHLJORGENSEN1986[113]	No measure of SMBG. Compared different insulin regimens
DAVIDSON 2003 [117]	Review. Used as a source of references.
DAVIDSON 2005A [116]	Review. Used as a source of references.
DAVIES 2004 [118]	Review. Used as a source of references.
DIMITRIADIS 1983[129]	Does not answer our question: timing of insulin administration and effect on hypoglycaemia.
DITZEL 1978 [130]	No investigation into SMBG
DOKUN 2010 [131]	Review. Used as a source of references.
FELDT-RASMUSSEN 1986 [147]	Investigation into different insulin regimens
FIALLO 2005[148]	Wrong population: children and young people. 8 point SMBG testing vs. CGMS: shows both methods gave similar mean bld glc. profiles and associations with HbA1c. CGMS may overestimate frequency of low glc. Levels, esp overnight.
FISCHL 2009[150]	Conference abstract. Got enough data already. See if now published.
FLOYD 2010A [152]	Abstract. Wrong comparison: CGM vs. SMBG
FOWLER 2000 [153]	Professionals' recommendations (survey

Reference	Reason for exclusion
	results): targets for SMBG
FRIEDRICH 2006 [154]	Short report about studies we have already included.
FULLERTON 2011[157]	Cochrane review protocol only.
GARG 2010B[159]	Publication of abstracts but all are type 2 diabetes or do not answer our question
GILDEN 1990 [166]	No relevant outcomes.
GIMENEIZ 2011A [168]	Wrong outcomes: atherosclerosis; wrong measurements: CGM derived blood glucose rather than SMBG.
GIMENEZ 2011[167]	Wrong outcomes: endothelial markers
GOMES 2011[175]	Conference abstract. Does not answer our question: HbA1c target rather than SMBG target.
GOMES 2012 [176]	Wrong population: all ages but no subgroup analysis. Shows increased SMBG leads to better HbA1c.
GREENHILL 2010 [181]	Overview of an already published trial which we have already included in our review.
GROSSI 2009 [186]	Wrong population: children. Shows that measuring 2 alternated daily preprandial mmts is better (reduction in HbA1c) than 2 alternate daily pre- and post-prandial mmts. However, both had a SS reducation on HbA1c.
HAFFNER 1991 [192]	No clear indication of changes in SMBG in response to intervention.
HANSEN 2009 [196]	Does not answer our question: correlations with number of tests for SMBG, rather than the other way around.(eg. People who are most likely to self-monitor. Aim was to find the most adherent types of patient.
HANSSEN 1994 [197]	Editorial comment.
HEMPE 2002A [203]	Included children and adolescents

Reference	Reason for exclusion
HINZMANN 2012 [211]	Review. Used as source of references.
HIRSH 2010A [212]	No investigation into SMBG
HOEY 2012 [215]	Review. Used as source of references.
HOME 2002 [219]	Review. Used as a source of references.
HORTENSIUS 2012B [225]	Professionals' recommendations: best frequency of SMBG.
JASPAN 1995 [234]	Review. Used as source of references.
KHAN 2006A[246]	Review. Used as source of references. Molecular targets, not blood glucose.
KILPATRICK 2006 [250]	Already got this study data (DCCT trial) SERVICE 2007 which had more detail so the SERVICE 2007 study was included rather than this one.
KILPATRICK 2007[251]	No relevant outcomes.
KILPATRICK 2007A [249]	Not a relevant measure: measured blood glucose variability
KILPATRICK 2008 [247]	DCCT trial results – wrong outcomes: cardiovascular
KILPATRICK 2009 [248]	Conference abstract. Got enough data already. See if now published.
KIRK 2010 [254]	Review. Used as a source of references.
KOLAWOLE 2005 [261]	Wrong population: type 2 diabetes.
KOLB 2010 [262]	Review. Used as a source of references.
KUMAR 2008 [270]	Wrong population: children and young people.
LAAKSO 2012[271]	Review. Used as a source of references.
LACHIN 2008 [272]	Investigation into DCCT trial data
LALIC 2012 [273]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (17%).
LAURITZEN 1983[279]	Investigation into different insulin regimens

Reference	Reason for exclusion
LAURITZEN 1985 [280]	Does not answer our question: does not look at targets or link targets or frequency to outcomes.
LEE 2011B [283]	Mixed population: % of type 1 diabetes not given. Guideline implementation study of glycaemic control
LEELARANTHA 2011[285]	Review. Used as source of references.
LEROITH 2005 [290]	Review. Used as source of references.
LIEBL 2009 [293]	Review. Used as source of references. All type 2 diabetes.
MAKINEN 2008A [302]	Does not answer our question: predictors of risk of diabetes complications but does not look at SMBG or blood glucose values.
MARCASON 2012 [306]	Short report; references cited are not clinical studies except Riddell 2011 which was CGM rather than SMBG.
MARTIN 2006[308]	8 year follow-up of patients
MAZZE 1995 [314]	Review of DCCT study. This study has already been included in this review.
MCCALL 2012 [315]	Review. Used as source of references.
MCCARTER 2006[318]	Not a relevant outcome: measured blood glucose variability
MCCARTY 1999 [319]	Does not answer our question: does not link SMBG to outcomes or look at targets.
MEHTA 2010 [326]	Review. Used as source of references.
MICOSSI 1988 [329]	Does not answer our question: treatment rather than self-monitoring.
MIGLIANI 2004[330]	Letter.
MILLER 2011[332]	Abstract. Full study available.
MOBERG 1993 [334]	No relevant outcomes
MOBERG 1994 [335]	Not a relevant outcome:

Reference	Reason for exclusion
	measured glucose variability
MONNIER 2003 [338]	Type 2 diabetic patients
MONNIER 2007[337]	No relevant outcomes.
MONTAGNANA 2009A [339]	Review. Used as a source of references.
MORELAND 2006 [341]	Generally shows increased monitoring leads to increased control but results for two of the groups have been combined together.
MOSS 1986 [344]	Review. Used as source of references.
NAU 2002 [366]	Does not answer our question: factors correlated with patient satisfaction.
NATHAN 2005[350]	Investigation into diabetes and cardiovascular disease
NICOLUCCI 1996[371]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (10 and 20%).
NYOMBA 2004 [377]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (56%). Additional study from old GL and cross-referencing SRs, MAs and other GLs
OTIENO 2002 [385]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (14%).
OTIM 1988 [386]	Wrong population: mixed population of adults and young people, but % adults not given.
PATRAKEEVA 2011 [395]	Conference abstract. Looks at CGM not SMBG.
PETERSON 1979 [400]	No investigation into SMBG.
PICCONI 2012 [403]	Review. Used as source of references.
PICKUP 2006 [405]	No difference in frequency of SMBG between the groups
PICHON 2011 [404]	Not in English.
PITSILLIDES 2011[409]	Wrong outcomes: insulin

Reference	Reason for exclusion
	sensitivity and epinephrine response during hypoglycaemia.
PURVIS 2013 [412]	Conference abstract. Wrong outcomes: such as macrovascular disease and CeVD.
RANKIN 2012 [415]	Interview with patients about blood glucose targets, but doesn't give specific targets.
RAYMAN 1984A [421]	Wrong question: SMBG by blood vs. urine.
REALSEN 2011 [422]	Review. Used as a source of references.
RENARD 2005 [426]	Review. Used as source of references.
ROSENSTOCK 2001 [436]	Review. Not about SMBG.
RUSNAK 2004 [440]	Overview of Canadian GL (they recommend measuring 3 times/day)
RUSSELL 2009 [443]	Review. Used as source of references.
RUSSELL 2009A[442]	Will be sued for technologies question.
SANTIPRABHOB 2008 [446]	Mixed population of children and adults, but <50% adults. Shows more frequent SMBG (3-4 times/day) leads to better HbA1c.
SARWAR 2010 [447]	Meta-analysis
SASTRE 2011 [448]	Conference abstract. Got enough data already. See if now published.
SAUNDERS 2009 [449]	Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes. Will be used for HbA1c question.
SCHNELL2009 [450]	Consensus statement: frequency and targets of SMBG.
SHALITIN 2009 [455]	Conference abstract. Got enough data already. See if now published.
SHALITIN 2010 [454]	Wrong population: mixed population of adults and children, but % adults not given. Seems to be more children because the mean

Reference	Reason for exclusion
	age is low. Shows SMBG linked to HbA1c target achievement
SHAMOON 1995 [456]	Already got this study data (DCCT trial) SERVICE 2007 which had more detail so the SERVICE 2007 and SERVICE 2001 study was included rather than this one.
SHICHIRI 2000 [459]	Type 2 diabetic patients
SIEGELAR 2010 [463]	Review. Used as source of references.
SIMINERIO 2012[464]	Short commentary on an study that has been published, which we have already included in this review.
SINGH 2008 [466]	Mixed population of type 1 diabetes and type 2 diabetes but no type 1 diabetes subgroup analysis and <70% type 1 diabetes (16%).
SLAMA 2006 [468]	Review. Used as source of references.
SPELLMANN 2009[470]	Review. Used as source of references.
SPOLLETT 2010 [471]	Review. Used as source of references.
STEELE 2010 [475]	Conference abstract. Wrong population: type 2 diabetes and non-diabetics.
STEELE 2011 [476]	Conference abstract. Wrong population: type 2 diabetes and non-diabetics.
STROWIG 1998 [481]	Does not address our question: meter with memory vs. meter with no memory
STUART 1995 [482]	Brief report.
SVENDSEN 1982[484]	Does not answer our question: does not link SMBG to outcomes.
SWIFT 2010 [485]	Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes. Wrong population: young people.
TAMBOLANE 2011 [487]	Conference abstract. Wrong population: young people.
THOMAS 2012 [492]	Wrong measurement – CGM

Reference	Reason for exclusion
	not SMBG. Shows need to take account of blood glucose variability.
VRIESENDORP2009[511]	Not a relevant outcome: measured glucose variability
WENG 2009 [517]	Conference abstract. Wrong outcomes – HbA1c targets.
WHITE 2008[519]	Follow-up data from DCCT
WHYTE 2013 [522]	Conference abstract. Wrong objective: two different self-testing tools.
WIKBLAD 1991 [525]	Wrong measurement – HbA1c and how it links to outcome, rather than SMBG linked to outcomes.
WINOCOUR 2003 [526]	Review. Used as source of references.
WORTH 1982A [529]	Does not measure frequency of SMBG
YEO 1985 [532]	Wrong population: type of diabetes not mentioned. Shows HBGM leads to decreased neuropathy and HbA1c compared to controls (no HBGM).
MILLER 2013 K. M. Miller, R. W. Beck, R. M. Bergenstal, R. S. Goland, M. J. Haller, J. B. McGill, H. Rodriguez, J. H. Simmons, and I. B. Hirsch. Evidence of a Strong Association Between Frequency of Self-Monitoring of Blood Glucose and Hemoglobin A1c Levels in T1D Exchange Clinic Registry Participants. *Diabetes Care* 36 (7):2009-2014, 2013.	Already included in original review.
ATAIE 2013 A. Ataie-Jafari, S.-C. Loke, A. B. Rahmat, B. Larijani, F. Abbasi, M. K. S. Leow, and Z. Yassin. A randomized placebo-controlled trial of alphacalcidol on the preservation of beta cell function in children with recent onset type 1 diabetes. *Clin.Nutr.* 32 (6):911-917, 2013.	Does not answer the question. Ordered by mistake.
BENNETT 2013 K. Bennett and F. Joseph. Diabetes requiring insulin - recent developments in management. *Prescriber* 24 (11):21-31, 2013.	Review
FULLERTON 2014 B Fullerton, K Jeitler, M Seitz, K Horvath, A Berghold, and A Siebenhofer. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2:CD009122, 2014.	Rv – used as source of references
GOMES 2013A MB. Gomes, AS de Mattos Matheus, LE Calliari, JL Luescher, TD Manna et al. Economic status and clinical care in young type 1 diabetes patients: a	Wrong population: young people/children

Reference	Reason for exclusion
nationwide multicenter study in Brazil. *Acta Diabetol.* 50 (5):743-752, 2013.	
HIRSCH 2014 I. B. Hirsch, S. N. DuBose, K. M. Miller, D. M. Maahs, and R. W. Beck. Twice daily versus once daily basal insulin does not result in better glycemic outcomes among MDI patients with T1D. *Diabetes Technol.Ther.* 16:A91, 2014.	Conference abstract (have enough fully published data on this already); for LA insulin once vs. twice question.
LEE 2014 WC Lee, E Smith, B Chubb, and M Lyng Wolden. Frequency of blood glucose testing among insulin-treated diabetes mellitus patients in the United Kingdom. *J Med Econ* 17 (3):167-175, 2014.	Does not answer the question: does not link frequency of tests with outcome.
MUCHMORE 1994 D. B. Muchmore, J. Springer, and M. Miller. Self-monitoring of blood glucose in overweight type 2 diabetic patients. *Acta Diabetol.* 31 (4):215-219, 1994.	Wrong population: type 2 diabetes
NATHAN 2014 D M. Nathan and DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 37 (1):9-16, 2014.	Does not answer the question: does not link SMBG mmts with outcome.
NATHAN 2014A DM. Nathan, Paula McGee, Michael W. Steffes, John M. Lachin, and DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. *Diabetes* 63 (1):282-290, 2014.	Does not answer the question: just shows association of HbA1c with outcome but does not give actual values of blood glucose.
ZOFFMANN 2014 V. Zoffmann, D. Vistisen, and M. Due-Christensen. A cross-sectional study of glycaemic control, complications and psychosocial functioning among 18- to 35-year-old adults with Type 1 diabetes. *Diabet.Med.* 31 (4):493-499, 2014.	Does not answer the question: links HbA1c with outcomes, not SMBG measurements.
DAVISON 2014 KA.K. Davison, CA. Negrato, R Cobas, A Matheus, L Tannus, CS. Palma, L Japiassu, JR.I. Carneiro, M Rodacki, et al., and Type Brazilian. Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: a nationwide survey in Brazil. *Nutr J* 13 (1):19, 2014.	Diets related to glycaemic control and CV risk factors. Does not give glycaemic control independently of diet and risk of CV.
CHANG 2014 A. Chang, K. Nakamura, T. Bailey, M. Christiansen, N. Bhavaraju, and D. Price. RT-CGM performance ready for independent diabetes management decisions. *Diabetes* 63:A214, 2014.	Conference abstract
CHAO 2014 J. H. Chao, A. Sussman, and I. B. Hirsch. Is sensible use of glycated albumin realistic in patients with diabetes mellitus-the sugar study. *J.Invest.Med.* 62	Conference abstract

Reference	Reason for exclusion
(1):204-205, 2014.	
CHOUDHARY 2013B P. Choudhary, S. Genovese, and G. Reach. Blood glucose pattern management in diabetes: Creating order from disorder. *J Diabetes Sci Technol* 7 (6):1575-1584, 2013.	Unable to get hold of article. SR so would only be used for checking refernces.
FLOYD 2012 B. Floyd, P. Chandra, S. Hall, C. Phillips, E. Alema-Mensah, G. Strayhorn, E. O. Ofili, and G. E. Umpierrez. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol* 6 (5):1094-1102, 2012.	Ordered for CGM (monitoring) question. Exclude from CGM question – SR/MA and used as source of references.
GOMES 2013B M. B. Gomes, R. A. Cobas, L. R. Tannus, A. S. Matheus, T. D. Manna, H. Pedrosa, M. Rodacki, A. Ramos, C. A. Negrato, and B. Tschiedel. Self-monitoring of blood glucose in type 1 diabetes patients in routine clinical care: A multicenter study in Brazil. *Diabetes Technol Ther* 15:A135, 2013.	Conference abstract
GURKOVA 2014 E Gurkova and K Ziakova. Self-care behaviour, treatment satisfaction and quality of life in people on intensive insulin treatment. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 158 (2):303-308, 2014.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
JUNQUIERA 2014 S. M. Junqueira, P. C. Andrade, C. V. Cachoeira, D. M. Repsold, and K. Sadik. Assessment of evidence on the effectiveness of self-monitoring blood glucose (SMBG) in diabetes patients treated with insulin in Latin America. *Value Health* 17 (3):A240, 2014.	Conference abstract
KAHLER 2014 P Kahler, B Grevstad, T Almdal, C Gluud, J Wetterslev, A Vaag, and B Hemmingsen. Targeting intensive versus conventional glycaemic control for type 1 diabetes mellitus: a systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. *BMJ open* 4 (8):e004806, 2014.	SR/MA – used as source of references.
LIU 2014 L. Liu, J. Yan, H. Deng, S. Lin, D. Yang, H. Ai, Y. Zhang, X. Zheng, B. Yao, G. Zhang, and J. Weng. A comparison between adult type 1 diabetic patients with optimal and poor glycemic control: Results from guangdong T1DM translational medicine study in china. *Diabetes* 63:A644, 2014.	Conference abstract
MORENO 2013 C. Moreno, L. Barros, C. Baptista, L. Ruas, M. Alves, S. Gouveia, J. Saraiva, D. Guelho, M. Carvalheiro, and F. Carrilho. Importance of retrospective continuous glucose monitoring in poorly controlled diabetic patients: A system that still has clinical usefulness. *Diabetes Technol Ther* 15:A67, 2013.	Conference abstract
TESTA 2014 M. A. Testa, J. K. Gill, M. Su, L. Traylor, and D. C. Simonson. CGM and SMBG	Conference abstract

Reference	Reason for exclusion
analytics predict hypoglycemic risk and symptoms during intensive insulin titration. *Diabetes* 63:A214, 2014.	
WHYTE 2013 M. B. Whyte, C. A. Manu, D. Hopkins, and S. Thomas. Evidence of patient self-testing at clinic review: Association with glycaemic control. *Diabet Med* 30:19-20, 2013.	Conference abstract

K.3.1 SMBG technologies

Reference	Reason for exclusion
Additional studies from old GL and cross-referencing SRs, MAs and other GLs	
AMBROSIADOU 1996 B. V. Ambrosiadou, D. G. Goulis, and C. Pappas. Clinical evaluation of the DIABETES expert system for decision support by multiple regimen insulin dose adjustment. Comput.Methods Programs Biomed. 49 (1):105-115, 1996.	Validation study – not our clinical outcomes.
ANGELES 2011 R. N. Angeles, M. I. Howard, and L. Dolovich. The effectiveness of web-based tools for improving blood glucose control in patients with diabetes Mellitus: A meta-analysis. Can.J.Diabetes 35 (4):344-352, 2011.	Used for references
ANON 2007A	Review – used for references
ARGENTO 2012 N. B. Argento, K. Nakamura, and R. Sala. HbA1c and mean glucose in insulin treated diabetes using the SevenPlus continuous glucose monitor (CGM): Correlation and intra-patient consistency over time. Diabetologia 55:S428-S429, 2012.	Conference abstract; Validation study – not clinical outcomes.
ARGENTO 2012A N. B. Argento, K. Nakamura, and R. D. Sala. A1C and Mean Glucose (MG) in insulin treated diabetes using the dexcom sevenplus Continuous Glucose Monitor (CGM): Correlation and intra-patient consistency over time. Diabetes 61:A1, 2012.	Conference abstract; Consistency study – not clinical outcomes.
ARSAND 2008 Eirik Arsand, James T. Tufano, James D. Ralston, and Per Hjortdahl. Designing mobile dietary management support technologies for people with diabetes. J.Telemed.Telecare 14 (7):329-332, 2008.	Usability study – not clinical outcomes.
ARSANO 2011	Conference abstract; overview of the technology, not clinical outcomes.
AUGUSTEIN 2007	Wrong population: mix of type 1 diabetes and type 2 diabetes but only 53% type 1 diabetes and no type 1 diabetes subgroup analysis.
BAGHURST 2011	Wrong population: children.
BARNARD 2011 Barnard, K., Parkin, C., and Ashraf, M. Use of an automated bolus calculator reduces fear of hypoglycaemia and improves confidence in dosage accuracy in type 1 diabetes mellitus patients treated with multiple daily insulin injections. Diabetologia 54, S410. 2011	Abstract – questionnaire to assess attitudes and behaviours with ABC
BARNARD 2012 Katharine Barnard, Christopher Parkin, Amanda Young, and Mansoor Ashraf. Use of an automated bolus calculator reduces fear of hypoglycemia and	Conference abstract; does not look at technologies.

Reference	Reason for exclusion
improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol 6 (1):144-149, 2012.	
BARNARD 2012 Katharine Barnard, Christopher Parkin, Amanda Young, and Mansoor Ashraf. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol 6 (1):144-149, 2012.	Survey based study. Not addressing specified outcomes
BELLAZZI 2002 R. Bellazzi, C. Larizza, S. Montani, A. Riva, M. Stefanelli, G. d'Annunzio, R. Lorini, E. J. Gomez, E. Hernando, E. Brugues, J. Cermeno, R. Corcoy, A. de Leiva, C. Cobelli, G. Nucci, S. Del Prato, A. Maran, E. Kilkki, and J. Tuominen. A telemedicine support for diabetes management: the T-IDDM project. Comput.Methods Programs Biomed. 69 (2):147-161, 2002.	Validation study – not clinical outcomes. Wrong population: children young people.
BENHAMOU 2007 P. Y. Benhamou, V. Melki, R. Boizel, F. Perreal, J. L. Quesada, S. Bessieres-Lacombe, J. L. Bosson, S. Halimi, and H. Hanaire. One-year efficacy and safety of Web-based follow-up using cellular phone in type 1 diabetic patients under insulin pump therapy: the PumpNet study. Diabetes Metab. 33 (3):220-226, 2007.	Not on new technology. Not addressing specified interventions/comparisons
BENHAMOU 2010A P.-Y. Benhamou, J.-L. Bosson, A. Penfornis, D. Dardari, S. Franc, P. Schaepelynck, B. Catargi, H. Hanaire, L. Chaillous, E. M. Renard, J.-L. Quesada, S. Halimi, and G. Charpentier. Telemedicine support using the DIABEO software on a smartphone improves HbA1c in poorly controlled type 1 diabetic patients: The randomised, 6-month, multicenter TeleDiab-1 trial. Diabetologia 53:S416, 2010.	Abstract – Telemedicine support
BERGENSTAL 2005A R. M. Bergenstal, R. L. Anderson, D. M. Bina, M. L. Johnson, J. L. Davidson, B. Solarz-Johnson, and D. M. Kendall. Impact of modem-transferred blood glucose data on clinician work efficiency and patient glycemic control. Diabetes Technol.Ther. 7 (2):241-247, 2005.	Wrong population: mix of type 1 diabetes and type 2 diabetes but <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
BLONDE 2006 L. Blonde and C. G. Parkin. Internet resources to improve health care for patients with diabetes. Endocr Pract 12 (SUPPL. 1):131-137, 2006.	Review. References are for websites that not for technologies that we are interested in; they are information websites.
BODE 2007	Not on new technology for SMBG. Not addressing review question.
BUCKINGHAM 2005 Bruce Buckingham, Jen Block, Jonathan Burdick, Andrea Kalajian, Craig Kollman, Michael Choy, Darrell M. Wilson, Peter Chase, and Diabetes Research in Children Network. Response to nocturnal alarms using a real-time glucose sensor. Diabetes Technol.Ther. 7 (3):440-447, 2005.	Wrong population: children and young people.

Reference	Reason for exclusion
BUCKINGHAM 2008 B. Buckingham. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr.Diabetes 9 (2):142-147, 2008.	Wrong population: children and young people.
BURSELL 2012 Sven Erik Bursell, Laima Brazionis, and Alicia Jenkins. Telemedicine and ocular health in diabetes mellitus. Clin Exp Optom 95 (3):311-327, 2012.	Review – used for references
CADUFF 2009 A. Caduff, M. S. Talary, M. Mueller, A. Megej, O. Defeo, P. Zakharov, S. Reinhard, M. Donath, J. Klisic, H.-J. Krebs, and W. A. Stahel. Application of a multisensor device for continuous glucose monitoring under home use conditions. Diabetes 58, 2009.	Conference abstract; Validation study – not clinical outcomes.
CADUFF 2011 A. Caduff, M. Mueller, A. Megej, F. Dewarrat, R. E. Suri, J. Klisic, M. Donath, P. Zakharov, D. Schaub, W. A. Stahel, and M. S. Talary. Characteristics of a multisensor system for non invasive glucose monitoring with external validation and prospective evaluation. Biosens.Bioelectron. 26 (9):3794-3800, 2011.	Validation study – not clinical outcomes.
CAMPOS 2010 Fabiola Campos-Cornejo, Daniel U. Campos-Delgado, Diego Espinoza-Trejo, Howard Zisser, Lois Jovanovic, Francis J. Doyle, and Eyal Dassau. An advisory protocol for rapid- and slow-acting insulin therapy based on a run-to-run methodology. Diabetes Technol.Ther. 12 (7):555-565, 2010.	Overview of the technology and simulated results, but not tested on pts for clinical outcomes.
CARRAL 2012 Sanlaureano F. Carral, P. Sanchez, and L. Lizan. Costs analysis of a mobile phone telemonitoring system for glycaemic control in patients with diabetes mellitus (DM) in spain: Preliminary results. Value Health 15 (7):A520, 2012.	Abstract– not clinical outcomes. Not specified interventions/comparisons
CARROLL 2007 Aaron E. Carroll, David G. Marrero, and Stephen M. Downs. The HealthPia GlucoPack Diabetes phone: a usability study. Diabetes Technol.Ther. 9 (2):158-164, 2007.	Wrong population: children and young people.
CAVAN 2013 D. A. Cavan, R. Ziegler, I. Cranston, K. Barnard, J. Ryder, C. Vogel, C. G. Parkin, B. Petersen, M. Schweitzer, and R. S. Wagner. Use of an automated bolus advisor improves glycaemic control without increased hypoglycaemia in patients with poorly controlled Type 1 and Type 2 diabetes treated with multiple daily insulin injection (MDI) therapy: First results from the Automated Bolus Advisor Control and Utility Study (ABACUS). Diabet.Med. 30:156, 2013.	Conference abstract – mixed population
CENGIZ 2011 Eda Cengiz, Jennifer L. Sherr, Stuart A. Weinzimer, and William V. Tamborlane. New-generation diabetes management: glucose sensor-	Review – used for references

Reference	Reason for exclusion
augmented insulin pump therapy. Expert Rev Med Devices 8 (4):449-458, 2011.	
CHAN 2012 Ka C. Chan, Lucia Wong, and David B. Chan. Design of a large scale community-based self-management system for diabetes mellitus. Stud Health Technol Inform 182:58-66, 2012.	Design of the technology but no clinical results.
CHARPENTIER 2011 Guillaume Charpentier, Pierre Yves Benhamou, Dured Dardari, Annie Clergeot, Sylvia Franc, Pauline Schaepelynck-Belicar, Bogdan Catargi, Vincent Melki, Lucy Chaillous, Anne Farret, Jean Luc Bosson, Alfred Penfornis, and TeleDiab Study Group. The Diabeo software enabling individualized insulin dose adjustments combined with telemedicine support improves HbA1c in poorly controlled type 1 diabetic patients: a 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes Care 34 (3):533-539, 2011.	Not addressing specified interventions/comparisons. REVIEW ON TELEMEDICINE
CHUANG 2004 Han Chuang, Elizabeth Taylor, and Thomas W. Davison. Clinical evaluation of a continuous minimally invasive glucose flux sensor placed over ultrasonically permeated skin. Diabetes Technol.Ther. 6 (1):21-30, 2004.	Validation study – not clinical outcomes.
DANNE 2009 T. Danne, H. W. de Valk, T. Kracht, K. Walte, R. Geldmacher, L. Solter, W. von dem Berge, Z. K. Welsh, J. R. Bugler, K. Lange, and O. Kordonouri. Reducing glycaemic variability in type 1 diabetes self-management with a continuous glucose monitoring system based on wired enzyme technology. Diabetologia 52 (8):1496-1503, 2009.	Not addressing specified interventions/comparisons
DOMINGUEZ 2011 M. E. Dominguez-Lopez, M. S. Ruiz De Adana, I. Gonzalez-Molero, M. Guerrero, I. Cardona, I. Sanchez, D. Fernandez, and F. Soriguer-Escofet. Clinical usefulness of a bolus calculator in patients with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion (CSII). Diabetes Technol.Ther. 13 (2):219, 2011.	Abstract– combination of SMBG and CGM
EDMONDS 1998 M. Edmonds, M. Bauer, S. Osborn, H. Lutfiyya, J. Mahon, G. Doig, P. Grundy, C. Gittens, G. Molenkamp, and D. Fenlon. Using the Vista 350 telephone to communicate the results of home monitoring of diabetes mellitus to a central database and to provide feedback. International journal of medical informatics 51 (2-3):117-125, 1998.	Age of participants not given, and unclear % of type 1 diabetes.
FACCHINETTI 2013 A. Facchinetti, G. Sparacino, S. Guerra, Y. M. Luijf, J. H. De Vries, J. K. Mader, M. Ellmerer, C. Benesch, L. Heinemann, D. Bruttomesso, A. Avogaro, and C. Cobelli. Real-time improvement of continuous glucose monitoring accuracy: The smart sensor concept. Diabetes Care 36 (4):793-800, 2013.	Not addressing specified interventions/comparisons. Not on SMBG
FARMER 2005A A. Farmer, O. J. Gibson, L. Tarassenko, and A. Neil. A systematic review of	SR used for references

Reference	Reason for exclusion
telemedicine interventions to support blood glucose self-monitoring in diabetes. Diabet.Med. 22 (10):1372-1378, 2005.	
FIORAVANTI 2011 A. Fioravanti, G. Fico, M. T. Arredondo, and J. P. Leuteritz. A mobile feedback system for integrated E-health platforms to improve self-care and compliance of diabetes mellitus patients. Annual International Conference of the IEEE Engineering in Medicine & Biology Society 2011:3550-3553, 2011.	METABO – overview of design but not clinical outcomes.
FRANC 2012A S. Franc, S. Borot, O. Ronsin, D. Dardari, C. Fagour, E. Renard, Leguerrier A. Marie, C. Vigeral, F. Moreau, P. Winiszewski, A. Vambergue, H. Mosnierpudar, L. Kessler, S. Reffet, B. Guerci, L. Millot, S. Halimi, C. Thivolet, J. L. Quesada, A. Clergeot, P. Schaepelynck-Belicar, B. Catargi, V. Melki, L. Chaillous, A. Farret, A. Penfornis, G. Charpentier, P.-Y. Benhamou, and H. Hanaire. Assessment of the relationship between the use of a telemedicine system and blood glucose control in patients with type 1 diabetes. Diabetes 61:A599, 2012.	Conference abstract - Telemedicine
FRANK 2011	Review used for references
FRANKLIN 2006 V. L. Franklin, A. W. Wilson, R. A. Butler, and S. A. Greene. A predictive tool for the self-management of diabetes (Librae): evaluation using a continuous glucose monitoring system. Diabet.Med. 23 (1):21-25, 2006.	Wrong population: mixed ages 7-21 years; % not given of adults. Low mean age, thus suggests mostly young people.
FRANKLIN 2008 Victoria Louise Franklin, Alexandra Greene, Annalu Waller, Stephen Alan Greene, and Claudia Pagliari. Patients' engagement with "Sweet Talk" - a text messaging support system for young people with diabetes. J Med Internet Res 10 (2):e20, 2008.	Wrong population: young people
FREEMAN 2010 J. E. Freeman, T. L. Rosser, M. Brown, T. M. J. Rosser, and J. F. Toy. USE of mobile phone technology to improve outcomes in patients with critical limb ischemia and diabetes. J.Am.Coll.Cardiol. 55 (10 SUPPL 1):A157, 2010.	Abstract–Not specified interventions/comparisons. Telemedicine
GARG 2004B Satish K. Garg, Sherwyn Schwartz, and Steven V. Edelman. Improved glucose excursions using an implantable real-time continuous glucose sensor in adults with type 1 diabetes. Diabetes Care 27 (3):734-738, 2004.	Not addressing specified interventions/comparisons
GIMINEZ 2002 Gabriel Gimenez-Perez, Maria Gallach, Edita Acera, Araceli Prieto, Olga Carro, Emilio Ortega, Jose Miguel Gonzalez-Clemente, and Didac Mauricio. Evaluation of accessibility and use of new communication technologies in patients with type 1 diabetes mellitus. J Med Internet Res 4 (3):E16, 2002.	Usability study – not clinical outcomes.
GOEDERT 2007 Joseph Goedert. Bringing I.T. into the home. Health Data Manag 15 (7):36-42, 2007.	Short report but no references.

Reference	Reason for exclusion
GREENE 2012 A. Greene, A. Shaltout, V. Alexander, M. Brillante, S. G. Cunningham, E. Fairley, N. Halawa, D. AlHuwail, D. Wake, R. R. McAlpine, and S. A. Greene. Integrating 'SweetText', a mobile phone behavioural support programme for young people with Type 1 diabetes, into clinical service in Kuwait and Scotland. Diabet.Med. 29:109, 2012.	Conference abstract; wrong population: young people.
HANAUER 2009 David A. Hanauer, Katherine Wentzell, Nikki Laffel, and Lori M. Laffel. Computerized Automated Reminder Diabetes System (CARDS): e-mail and SMS cell phone text messaging reminders to support diabetes management. Diabetes Technol.Ther. 11 (2):99-106, 2009.	Wrong population. Not addressing specified technologies.
HARNO 2006 Kari Harno, Ritva Kauppinen-Makelin, and Juha Syrjalainen. Managing diabetes care using an integrated regional e-health approach. J.Telemed.Telecare 12 Suppl 1:13-15, 2006.	Supplementary information from an already published SR.
HARVEY 2012 Rebecca A. Harvey, Eyal Dassau, Howard C. Zisser, Wendy Bevier, Dale E. Seborg, Lois Jovanovic, and Francis J. Doyle. Clinically relevant hypoglycemia prediction metrics for event mitigation. Diabetes Technol.Ther. 14 (8):719-727, 2012.	Validation study – not clinical outcomes.
HERBRECHTSMEIER 2009 P. Herbrechtsmeier, A. J. Mueller, C. Hasslacher, and G. U. Auffarth. New optical method for blood glucose self-monitoring. Diabetologia 52 (S1):S367, 2009.	Conference abstract; Validation study – not clinical outcomes.
HILL 2013 J. Hill and M. G. Masding. The development of an innovative mobile phone App for Type 1 diabetes alcohol education. Diabet.Med. 30:112, 2013.	Conference abstract; development of an app, not tested yet.
HIRSCH 2004 Irl B. Hirsch. Blood glucose monitoring technology: translating data into practice. Endocr Pract 10 (1):67-76, 2004.	Review with N=3 case reports included. Used as a source of references.
HIRSCH 2008 I. B. Hirsch, J. Abelseth, B. W. Bode, J. S. Fischer, F. R. Kaufman, J. Mastrototaro, C. G. Parkin, H. A. Wolpert, and B. A. Buckingham. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol.Ther. 10 (5):377-383, 2008.	Review – used for references
HOLTZ 2012 Bree Holtz and Carolyn Lauckner. Diabetes management via mobile phones: a systematic review. Telemed J E Health 18 (3):175-184, 2012.	Used for references
HOMAN 1996 R. R. Holman, A. D. Smale, E. Pemberton, A. Riefflin, and J. L. Nealon.	Age not given. Handheld insulin regimen optimiser.

Reference	Reason for exclusion
Randomized controlled pilot trial of a hand-held patient-oriented, insulin regimen optimizer. Medical informatics = Médecine et informatique 21 (4):317-326, 1996.	
HUSSEIN 2011 Wiam I. Hussein, Khadija Hasan, and Ahmed A. Jaradat. Effectiveness of mobile phone short message service on diabetes mellitus management; the SMS-DM study. Diabetes Res.Clin.Pract. 94 (1):e24-e26, 2011.	Wrong population: type 2 diabetes
ILIOPOULOU2005 D. Iliopoulou, K. Giokas, S. Mougiakakou, J. Stoitsis, A. Prentza, and K. Nikita. A telematic system for diabetes management, reporting and patient advice. J.Inf.Technol.Healthc. 3 (5):307-313, 2005.	No UK location and no reply from either publisher or author.
ISTEPANIAN 2009 Robert S. H. Istepanian, Karima Zitouni, Diane Harry, Niva Moutosammy, Ala Sungoor, Bee Tang, and Kenneth A. Earle. Evaluation of a mobile phone telemonitoring system for glycaemic control in patients with diabetes. J.Telemed.Telecare 15 (3):125-128, 2009.	Wrong population: mix of type 1 diabetes and type 2 diabetes but only 8% type 1 diabetes type 1 diabetes and no type 1 diabetes subgroup analysis.
IZQUIERDO 2007 R. Izquierdo, S. Meyer, J. Starren, R. Goland, J. Teresi, S. Shea, and R. S. Weinstock. Detection and remediation of medically urgent situations using telemedicine case management for older patients with diabetes mellitus. Therapeutics and Clinical Risk Management 3 (3):485-489, 2007.	Not addressing specified interventions/comparisons. REVIEW ON TELEMEDICINE
KAUFMAN 2012 N. Kaufman. Using health information technology to prevent and treat diabetes. Int.J.Clin.Pract. 66 (SUPPL. 175):40-48, 2012.	Review with conference abstracts - used for references
KLUPA 2008 T. Klupa, T. Benbenek-Klupa, M. Malecki, M. Szalecki, and J. Sieradzki. Clinical usefulness of a bolus calculator in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. J Int Med Res 36 (5):1112-1116, 2008.	Not specified interventions/comparison. Result data not reported.
KLUPA 2009 T. Klupa, K. Cyganek, B. Katra, J. Skupien, J. Sieradzki, and M. T. Malecki. The dual-wave bolus feature in T1DM adult users of insulin pumps. Diabetes 58, 2009.	Conference abstract; outside of the scope – looks at a new type of pump.
KOURIS 2010 Ioannis Kouris, Stavroula Mougiakakou, Luca Scarnato, Dimitra Iliopoulou, Peter Diem, Andriani Vazeou, and Dimitris Koutsouris. Mobile phone technologies and advanced data analysis towards the enhancement of diabetes self-management. Int.j.electron.healthc. 5 (4):386-402, 2010.	Used for reference
KOVATCHEV 2004 Boris P. Kovatchev, Linda A. Gonder-Frederick, Daniel J. Cox, and William L. Clarke. Evaluating the accuracy of continuous glucose-monitoring sensors: continuous glucose-error grid analysis illustrated by TheraSense Freestyle	Accuracy study not clinical outcomes. Trial on this has already been published (FELDMAN 2003) and we

Reference	Reason for exclusion
Navigator data. Diabetes Care 27 (8):1922-1928, 2004.	have included this study in this review.
KUMAR 2004 V. S. Kumar, K. J. Wentzell, T. Mikkelsen, A. Pentland, and L. M. Laffel. The daily (Daily Automated Intensive Log for Youth) trial: A wireless, portable system to improve adherence and glycemic control in youth with diabetes. Diabetes Technol.Ther. 6 (4):445-453, 2004.	Wrong population: children and young people.
LADYZYNSKI 2007 P. Ladyzynski and J. M. Wójcicki. Home telecare during intensive insulin treatment--metabolic control does not improve as much as expected. J.Telemed.Telecare 13 (1):44-47, 2007.	Wrong population: pregnant type 1 diabetes women.
LEHMANN 1998 E. D. Lehmann. Preliminary experience with the Internet release of AIDA--an interactive educational diabetes simulator. Comput.Methods Programs Biomed. 56 (2):109-132, 1998.	Wrong outcomes: qualitative experiences of using AIDA interactive diabetes educational tool.
LEHMANN 1999 E. D. Lehmann. Experience with the Internet release of AIDA v4.0--http://www.diabetic.org.uk.aida.htm--an interactive educational diabetes simulator. Diabetes Technol.Ther. 1 (1):41-54, 1999.	Overview of AIDA and a few case reports.
LEU 2005 M. G. Leu, T. E. Norris, J. Hummel, M. Isaac, and M. W. Brogan. A randomized, controlled trial of an automated wireless messaging system for diabetes. Diabetes Technol.Ther. 7 (5):710-718, 2005.	Wrong population: mix of type 1 diabetes and type 2 diabetes but only 26% type 1 diabetes and no type 1 diabetes subgroup analysis.
LEVINE 2009 Betty A. Levine, Jeanine Warisse Turner, James D. Robinson, Pamela Angelus, and Tang Ming-Jye Hu. Communication plays a critical role in web-based monitoring. J Diabetes Sci Technol 3 (3):461-467, 2009.	Unclear diabetes population – mix of type 1 diabetes and type 2 diabetes but % unclear and no type 1 diabetes subgroup analysis.
LIANG 2010 X. H. Liang, Q. Q. Wang, X. L. Yang, J. Cao, J. C. Chen, X. B. Mo, J. F. Huang, L. Wang, and D. F. Gu. Effect of mobile phone intervention for diabetes self-management support on glycemic control: A meta-analysis. Cardiology 117:120, 2010.	Conference abstract. Now published (LIANG 2011).
LIANG 2011 X. Liang, Q. Wang, X. Yang, J. Cao, J. Chen, X. Mo, J. Huang, L. Wang, and D. Gu. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet.Med. 28 (4):455-463, 2011.	SR not addressing specified interventions/comparisons
LIBERMAN 2011 A. Liberman, B. Buckingham, and M. Phillip. Diabetes technology and the human factor. Int.J.Clin.Pract.Suppl. (170):83-90, 2011.	Review with conference abstracts used for references
LUNN 2011 D. J. Lunn, C. Wei, and R. Hovorka. Fitting dynamic models with forcing	Uses virtual data – not tested on pts and thus not

Reference	Reason for exclusion
functions: Application to continuous glucose monitoring in insulin therapy. Stat.Med. 30 (18):2234-2250, 2011.	real clinical outcomes.
MALJANIAN 2005 R. Maljanian, N. Grey, I. Staff, and L. Conroy. Intensive telephone follow-up to a hospital-based disease management model for patients with diabetes mellitus. Disease management 8 (1):15-25, 2005.	Wrong population: mix of type 1 diabetes and type 2 diabetes but only 4% type 1 diabetes and no type 1 diabetes subgroup analysis.
MARRERO 1989 D. G. Marrero, K. K. Kronz, M. P. Golden, J. C. Wright, D. P. Orr, and N. S. Fineberg. Clinical evaluation of computer-assisted self-monitoring of blood glucose system. Diabetes Care 12 (5):345-350, 1989.	Wrong population: young people and adults but low mean age, thus suggests mostly young people! Old technology (1989 study).
MARTINEZ 2011 Inaki Martinez-Sarriegui, Gema Garcia-Saez, Mercedes Rigla, Eulalia Brugues, Alberto de Leiva, Enrique J. Gomez, and Elena M. Hernando. How continuous monitoring changes the interaction of patients with a mobile telemedicine system. J Diabetes Sci Technol 5 (1):5-12, 2011.	Not addressing specified interventions/comparisons. REVIEW ON TELEMEDICINE
MASTROTOTARO 2009 John Mastrototaro and Scott Lee. The integrated MiniMed Paradigm REAL-Time insulin pump and glucose monitoring system: implications for improved patient outcomes. Diabetes Technol.Ther. 11 Suppl 1:S37-S43, 2009.	Review – used for references
MCCARRIER 2009 K. P. McCarrier, J. D. Ralston, I. B. Hirsch, G. Lewis, D. P. Martin, F. J. Zimmerman, and H. I. Goldberg. Web-based collaborative care for type 1 diabetes: a pilot randomized trial. Diabetes Technol.Ther. 11 (4):211-217, 2009.	Not addressing specified technologies
MCCLAIN 2010 I. McClain and E. Thompson. The use of cell phone technology provides teens more control and independence and healthcare cost savings in the management of chronic disease. Perspect Health Inf Manag 7:1g, 2010.	Opinion article/review.
MCKENZIE 2011 L. McKenzie, A. Tasker, and S. Greene. Telemedicine delivered interpretation and improvement using a standardised protocol, for continuous glucose monitoring with multiple daily injections or pump therapy. Pediatr.Diabetes 12:126, 2011.	Conference abstract. Wrong population: children young people.
MEYERHOFF 1994 C. Meyerhoff, F. Bischof, and E. F. Pfeiffer. Long-term experiences with a computerized diabetes management and glucose monitoring system in insulin-dependent diabetic patients. Diabetes Res.Clin.Pract. 24 (1):1-7, 1994.	Not on new technology. Not addressing specified interventions/comparisons
MIELE 2012 Anthony Miele, Karen Weiland, and Kathleen M. Dungan. Clinical outcomes associated with referral-based continuous glucose monitoring using a central standardized interpretation strategy. Diabetes Technol.Ther. 14 (9):765-771, 2012.	Wrong intervention: centralised process for analysing and interpreting CGM results.

Reference	Reason for exclusion
MORRISH 1989 N. J. Morrish, D. L. Cohen, B. Hicks, and H. Keen. A controlled study of the effect of computer-aided analysis of home blood glucose monitoring on blood glucose control. Diabet.Med. 6 (7):591-594, 1989.	Not addressing specified interventions and comparisons.
MOSER 2012 Emily G. Moser, Audrey A. Morris, and Satish K. Garg. Emerging diabetes therapies and technologies. Diabetes Res.Clin.Pract. 97 (1):16-26, 2012.	Review – used for references
MOUGIAKOKOU 2010 Stavroula G. Mougiakakou, Christos S. Bartsocas, Evangelos Bozas, Nikos Chaniotakis, Dimitra Iliopoulou, Ioannis Kouris, Sotiris Pavlopoulos, Aikaterini Prountzou, Marios Skevofilakas, Alexandre Tsoukalis, Kostas Varotsis, Andrianni Vazeou, Konstantia Zarkogianni, and Konstantina S. Nikita. SMARTDIAB: a communication and information technology approach for the intelligent monitoring, management and follow-up of type 1 diabetes patients. IEEE Trans Inf Technol Biomed 14 (3):622-633, 2010.	Validation study of SMARTDIAB – not clinical outcomes. Pilot clinical trial underway (not yet published)
NELSON 1983 J. D. Nelson, M. A. Woelk, and S. Sheps. Self glucose monitoring: A comparison of the glucometer, glucoscan, and hypocount B. Diabetes Care 6 (3):262-267, 1983.	Unclear diabetes population.
NOH 2010 Jung Hyun Noh, Young Jung Cho, Hong Woo Nam, Jung Han Kim, Dong Jun Kim, Hye Sook Yoo, Young Woo Kwon, Mi Hye Woo, Jae Won Cho, Myeong Hee Hong, Joo Hwa Yoo, Min Jeong Gu, Soon Ai Kim, Kyung Eh An, Soo Mi Jang, Eun Kyung Kim, and Hyung Joon Yoo. Web-based comprehensive information system for self-management of diabetes mellitus. Diabetes Technol.Ther. 12 (5):333-337, 2010.	Wrong population: type 2 diabetes
NYOMBA 2004 B. L. G. Nyomba, L. Berard, and L. J. Murphy. Facilitating access to glucometer reagents increases blood glucose self-monitoring frequency and improves glycaemic control: a prospective study in insulin-treated diabetic patients. Diabet.Med. 21 (2):129-135, 2004.	Wrong population: mix of type 1 diabetes and type 2 diabetes but only 56% type 1 diabetes and no type 1 diabetes subgroup analysis.
OGRADY 2012 Michael J. O'Grady, Adam J. Retterath, D. Barry Keenan, Natalie Kurtz, Martin Cantwell, Glenn Spital, Michael N. Kremliovsky, Anirban Roy, Elizabeth A. Davis, Timothy W. Jones, and Trang T. Ly. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. Diabetes Care 35 (11):2182-2187, 2012.	Wrong population: young people and young adults but very low median age, thus suggests mostly young people!
OKAZAKI 2012 Shintaro Okazaki, Jose Alberto Castaneda, Silvia Sanz, and Jorg Henseler. Factors affecting mobile diabetes monitoring adoption among physicians: questionnaire study and path model. J Med Internet Res 14 (6):e183, 2012.	Physicians' opinions of smartphone monitoring adoption – not tested on pts or show clinical outcomes.
PAISLEY 2011	Conference abstract; wrong

Reference	Reason for exclusion
A. N. Paisley and R. J. Young. Use of a telehealth device for the management of blood sugar control in patients with Type 1 diabetes. Diabet.Med. 28:167, 2011.	population: pregnant or post-natal type 1 diabetes women.
PELZER 2011 Ruaan Pelzer, Edward H. Mathews, and Leon Liebenberg. Preliminary application of a new bolus insulin model for type 1 diabetes. Diabetes Technol.Ther. 13 (5):527-535, 2011.	Not addressing intervention/ comparisons
PULMAN 2013 A. J. Pulman, J. Hill, and M. G. Masding. Why haven't YOU thought of that? Over 15 great mobile App ideas for improving the quality of life of a young person with Type 1 diabetes. Diabet.Med. 30:112, 2013.	Conference abstract; ideas of young people, not clinical outcomes.
RECUPERO 2013 Anthony Recupero, Becket Mahnke, and Jordan E. Pinsker. Emerging technology in diabetes care: the real-time diabetes monitoring system. Mil Med 178 (2):218-221, 2013.	Overview of the technology, not clinical outcomes.
REED 2005 Karen Reed and Eldon D. Lehmann. Diabetes website review: www.2aida.org. Diabetes Technol.Ther. 7 (5):741-754, 2005.	Review of the AIDA website.
RIGLA 2007 Mercedes Rigla, M. Elena Hernando, Enrique J. Gomez, Eulalia Brugues, Gema Garcia-Saez, Veronica Torralba, Agustina Prados, Luisa Erdozain, Joana Vilaverde, and Alberto de Leiva. A telemedicine system that includes a personal assistant improves glycemic control in pump-treated patients with type 1 diabetes. J Diabetes Sci Technol 1 (4):505-510, 2007.	Not addressing specified interventions/comparisons. REVIEW ON TELEMEDICINE
RIGLA 2008 M. Rigla, M. E. Hernando, E. J. GóMez, E. Brugués, G. García-Sáez, I. Capel, B. Pons, and A. Leiva. Real-time continuous glucose monitoring together with telemedical assistance improves glycemic control and glucose stability in pump-treated patients. Diabetes Technol.Ther. 10 (3):194-199, 2008.	Not addressing specified interventions/comparisons. REVIEW ON TELEMEDICINE
RILEY 2011 W. T. Riley, D. E. Rivera, A. A. Atienza, W. Nilsen, S. M. Allison, and R. Mermelstein. Health behavior models in the age of mobile interventions: Are our theories up to the task? Transl.Behav.Med. 1 (1):53-71, 2011.	Review – used for references
ROSENFALCK 1993A A. M. Rosenfalck and I. Bendtson. The Diva(™) system, a computerized diary, used in young type 1 diabetic patients. DIABETE METABOL. 19 (1):25-29, 1993.	Wrong population: mixed ages 14-20 years; % not given of adults. Low mean age, thus suggests mostly young people!
ROSSI 2009 Maria C. E. Rossi, Antonio Nicolucci, Fabio Pellegrini, Daniela Bruttomesso, Paolo Di Bartolo, Giuseppe Marelli, Michela Dal Pos, Marianna Galetta, David Horwitz, and Giacomo Vespasiani. Interactive diary for diabetes: A useful and easy-to-use new telemedicine system to support the decision-making	TELEMEDICINE – not addressing specified interventions/comparisons

Reference	Reason for exclusion
process in type 1 diabetes. Diabetes Technol.Ther. 11 (1):19-24, 2009.	
ROSSI 2012 M. C. Rossi, A. Nicolucci, G. Lucisano, Bartolo P. Di, V. Miselli, R. Anichini, and G. Vespasiani. "Diabetes Interactive Diary" Telemedicine System vs. Standard Carbohydrate Counting Education in Type 1 Diabetes: Results of a randomized trial. Diabetes 61:A292, 2012.	Abstract – mixed interventions (electronic diary/bolus calculator/telemedicine)
ROTHERAM 2012 Mary Jane Rotheram-Borus, Mark Tomlinson, Margaret Gwegwe, W. Scott Comulada, Neal Kaufman, and Marion Keim. Diabetes buddies: peer support through a mobile phone buddy system. Diabetes Educ. 38 (3):357-365, 2012.	Unclear diabetes population: seems to be type 2 diabetes as all pts are severely obese.
RUTSCHER 1990 A. Rutscher, E. Salzsieder, U. Thierbach, U. Fischer, and G. Albrecht. KADIS--a computer-aided decision support system for improving the management of type-I diabetes. Exp Clin Endocrinol 95 (1):137-147, 1990.	Only tested on N=1 patient.
RUTSCHER 1994 A. Rutscher, E. Salzsieder, and U. Fischer. KADIS: model-aided education in type I diabetes. Karlsburg Diabetes Management System. Comput.Methods Programs Biomed. 41 (3-4):205-215, 1994.	Overview of the technology but not tested on pts for clinical outcomes.
SALZSIEDER 1990A E. Salzsieder, U. Fischer, H. Stoewhas, U. Thierbach, A. Rutscher, R. Menzel, and G. Albrecht. A model-based system for the individual prediction of metabolic responses to improve the therapy in type I diabetes. Horm.Metab.Res. 24 (SUPPL.):10-19, 1990.	Not on new technology. Not addressing specified interventions/comparisons
SHAPIRA 2010 Gali Shapira, Ofer Yodfat, Arava HaCohen, Paul Feigin, and Richard Rubin. Bolus guide: a novel insulin bolus dosing decision support tool based on selection of carbohydrate ranges. J Diabetes Sci Technol 4 (4):893-902, 2010.	Not addressing specified outcomes/interventions/comparisons
SIRIWARDENA 2012 L. S. A. N. Siriwardena, W. A. S. Wickramasinghe, K. L. D. Perera, Rohana B. Marasinghe, Prasad Katulanda, and Roshan Hewapathirana. A review of telemedicine interventions in diabetes care. J.Telemed.Telecare 18 (3):164-168, 2012.	Review used for references
SIVANANTHAN 2011 Sampath Sivananthan, Valeriya Naumova, Chiara Dalla Man, Andrea Facchinetti, Eric Renard, Claudio Cobelli, and Sergei V. Pereverzyev. Assessment of blood glucose predictors: the prediction-error grid analysis. Diabetes Technol.Ther. 13 (8):787-796, 2011.	Validation study – not clinical outcomes.
SKROVSETH 2012A Stein Olav Skrovseth, Eirik Arsand, Fred Godtliebsen, and Gunnar Hartvigsen. Mobile phone-based pattern recognition and data analysis for patients with type 1 diabetes. Diabetes Technol.Ther. 14 (12):1098-1104, 2012.	Not addressing specified interventions/comparisons

Reference	Reason for exclusion
SKROVSETH 2013 Stein Olav Skrovseth, Eirik Arsand, Fred Godtliebsen, and Ragnar M. Joakimsen. Model-driven diabetes care: study protocol for a randomized controlled trial. Trials 14:139, 2013.	Protocol of upcoming trial not full trial results.
SOZZI 1998 S. Sozzi, T. Strack, M. Schulz, and A. M. Albisser. Compliance in microcomputer-assisted conventional insulin therapy: computer simulation study results. Am J Physiol 254 (2 Pt 1):E237-E242, 1988.	Uses virtual /computer simulated data – not tested on pts and thus not real clinical outcomes.
SUTCLIFFE 2011 P. Sutcliffe, S. Martin, J. Sturt, J. Powell, F. Griffiths, A. Adams, and J. Dale. Systematic review of communication technologies to promote access and engagement of young people with diabetes into healthcare. BMC Endocr.Disord. 11 (1), 2011.	Used for references
TANI 2010 Shoko Tani, Terutaka Marukami, Atsuko Matsuda, Akiko Shindo, Keiko Takemoto, and Hiroshi Inada. Development of a health management support system for patients with diabetes mellitus at home. J Med Syst 34 (3):223-228, 2010.	Validation study – not clinical outcomes. Unclear diabetes population.
TASKER 2007 Anthony P. B. Tasker, Lorna Gibson, Victoria Franklin, Peter Gregor, and Stephen Greene. What is the frequency of symptomatic mild hypoglycemia in type 1 diabetes in the young?: assessment by novel mobile phone technology and computer-based interviewing. Pediatr.Diabetes 8 (1):15-20, 2007.	Wrong population: children and young people.
TO 2011 W. J. To, J. Wakizaka, P. Chen, and A. Cheung. Point-of-care technology for early detection of Diabetes Mellitus. FASEB J. 25, 2011.	Conference abstract; not SMBG measures, but conjunctival microcirculation
TUBIANA 2007 N. Tubiana-Rufi, J. P. Riveline, and D. Dardari. Real-time continuous glucose monitoring using GuardianRT: from research to clinical practice. Diabetes Metab. 33 (6):415-420, 2007.	used for references
UNGER 2007 J. Unger. Fine-tuning glycemic control using computerized downloading software: A case-based approach. Endocrinol.Metab.Clin.North Am. 36 (SUPPL. 2):27-45, 2007.	Case studies, only 1 type 1 diabetes patient.
UPADHYAY 2007 Neil Upadhyay, Kokot Mateja Kokalj, Kokot Matej Kokalj, Josip Car, and Igor Svab. Mobile phone messaging - a telemedicine for people with diabetes mellitus. Cochrane Database Syst Rev Issue 1:CD006393, 2007.	Cochrane review protocol of telemedicine via mobile phone messaging. Results not published yet.
VAHATALO 2004 M. A. Vahatalo, H. E. Virtamo, J. S. Viikari, and T. Ronnemaa. Cellular phone transferred self blood glucose monitoring: Prerequisites for positive	Not addressing specified interventions and comparisons.

Reference	Reason for exclusion
outcome. Pract.Diabetes Int. 21 (5):192-194, 2004.	
VIGERSKY 2003 Robert A. Vigersky, Eric Hanson, Edward McDonough, Timothy Rapp, John Pajak, and Robert S. Galen. A wireless diabetes management and communication system. Diabetes Technol.Ther. 5 (4):695-702, 2003.	Overview of the technology but not tested on pts for clinical outcomes.
WANBERG 2006 Silje C. Wangberg, Eirik Arsand, and Niklas Andersson. Diabetes education via mobile text messaging. J.Telemed.Telecare 12 Suppl 1:55-56, 2006.	Supplementary information to a review article.
WEI 2011 Igor Wei, Yannis Pappas, Josip Car, Aziz Sheikh, and Azeem Majeed. Computer-assisted versus oral-and-written dietary history taking for diabetes mellitus. Cochrane Database Syst Rev Issue 12:CD008488, 2011.	Wrong intervention: patient history-taking system rather than SMBG.
WEISSMANN 2012 J. Weissmann, A. Muller, K. Pralle, H.-J. Ruessmann, B. Gregersen, D. Messinger, and I. Amann-Zalan. Information management improves medical outcome and supports therapy decision in diabetes care: Results from the multicenter observational VISION study. Diabetologia 55:S425, 2012.	Abstract – mixed population (type 1 diabetes and type 2 diabetes)
WEITZMAN 2011 Elissa R. Weitzman, Skyler Kelemen, and Kenneth D. Mandl. Surveillance of an Online Social Network to Assess Population-level Diabetes Health Status and Healthcare Quality. Online j.public health inform. 3 (3), 2011.	Mixed population (type 1 diabetes & type 2 diabetes). Not addressing specified interventions/comparisons
WEITZMAN 2013 Elissa R. Weitzman, Skyler Kelemen, Maryanne Quinn, Emma M. Eggleston, and Kenneth D. Mandl. Participatory surveillance of hypoglycemia and harms in an online social network. JAMA Intern Med 173 (5):345-351, 2013.	Survey for surveillance/information, rather than helping an individual's SMBG.
WELCH 2006A G. Welch and R. Shayne. Interactive behavioral technologies and diabetes self-management support: Recent research findings from clinical trials. Curr Diab Rep 6 (2):130-136, 2006.	Review – used for references
WILLIAMS 1996 A. G. Williams. Insulin algorithms in the self-management of insulin-dependent diabetes: the interactive 'Apple Juice' program. Med Inform (Lond) 21 (4):327-344, 1996.	Review of the 'apple juice' programme designed for children, with N=1 case reports included. Used as a source of references.
WOOD 2007 Jamie R. Wood and Lori M. B. Laffel. Technology and intensive management in youth with type 1 diabetes: state of the art. Curr Diab Rep 7 (2):104-113, 2007.	Review – used for references
ZISSER 2008 Howard Zisser, Lauren Robinson, Wendy Bevier, Eyal Dassau, Christian Ellingsen, Francis J. Doyle, and Lois Jovanovic. Bolus calculator: a review of	Review – used for references

Reference	Reason for exclusion
four "smart" insulin pumps. Diabetes Technol.Ther. 10 (6):441-444, 2008.	
ZISSER 2010 Howard Zisser, Robin Wagner, Stefan Pleus, Cornelia Haug, Nina Jendrike, Chris Parkin, Matthias Schweitzer, and Guido Freckmann. Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison. Diabetes Technol.Ther. 12 (12):955-961, 2010.	No comparative arm.
ZISSER 2012A	Conference abstract
ZIEGLER 2013 Ralph Ziegler, David A. Cavan, Iain Cranston, Katharine Barnard, Jacqueline Ryder, Claudia Vogel, Christopher G. Parkin, Walter Koehler, Iris Vesper, Bettina Petersen, Matthias A. Schweitzer, and Robin S. Wagner. Use of an Insulin Bolus Advisor Improves Glycemic Control in Multiple Daily Insulin Injection (MDI) Therapy Patients With Suboptimal Glycemic Control: First results from the ABACUS trial. Diabetes Care, 2013.	Wrong comparison: Bolus vs. manual calculation. Has been included in the carbohydrate counting review (technologies aiding carb counting)
SKROVSETH 2012 SO Skrovseth, Eirik Arsand, Fred Godtliebsen, and Ragnar M. Joakimsen. Model driven mobile care for patients with type 1 diabetes. *Stud Health Technol Inform* 180:1045-1049, 2012.	Wrong intervention: mobile phone apps.
REICHEL 2013 A Reichel, H Rietzsch, B Ludwig, K Rothig, A Moritz, and SR. Bornstein. Self-adjustment of insulin dose using graphically depicted self-monitoring of blood glucose measurements in patients with type 1 diabetes mellitus. *J Diabetes Sci Technol* 7 (1):156-162, 2013.	Article unavailable.
Study for education review **ROSSI 2012** M. C. Rossi, A. Nicolucci, G. Lucisano, Bartolo P. Di, V. Miselli, R. Anichini, and G. Vespasiani. "Diabetes Interactive Diary" Telemedicine System vs. Standard Carbohydrate Counting Education in Type 1 Diabetes: Results of a randomized trial. *Diabetes* 61:A292, 2012.	Ordered for a different review (education)
BARNARD 2012 K. Barnard, C. Parkin, A. Young, and M. Ashraf. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. *J Diabetes Sci Technol* 6 (1):144-149, 2012.	Already found study in pre-reruns literature. Was excluded due to being a survey-based study, and not addressing our pre-specified outcomes.
BRANCATO 2014 D. Brancato, A. Scorsone, L. Spano, S. Ferranti, M. Fleres, L. Ferrara, V. Aiello, G. Saura, Noto A. Di, C. Calandrino, and V. Provenzano. Effectiveness of the glucometer with bolus calculator in adults with type 1 diabetes. *Ital.J.Med.* 8:16, 2014.	Conference abstract
CAVAN 2013A D. A. Cavan, R. Ziegler, I. Cranston, K. Barnard, J. Ryder, C. Vogel, C. G. Parkin,	Conference abstract

Reference	Reason for exclusion
B. Petersen, M. Schweitzer, and R. S. Wagner. Use of an automated bolus advisor improves glycaemic control without increased hypoglycaemia in patients with poorly controlled Type 1 and Type 2 diabetes treated with multiple daily insulin injection (MDI) therapy: First results from the Automated Bolus Advisor Control and Utility Study (ABACUS). *Diabet.Med.* 30:156, 2013.	
CAVAN 2013 D. A. Cavan, R. Ziegler, I. Cranston, K. Barnard, C. G. Parkin, W. Koehler, B. Petersen, I. Vesper, M. A. Schweitzer, and R. S. Wagner. Use of an automated bolus advisor improves multiple outcomes in patients treated with multiple daily insulin injections: Results from ABACUS. *Diabetologia* 56:S425, 2013.	Conference abstract
CAVAN 2014 DA. Cavan, R Ziegler, I Cranston, K Barnard, J Ryder, C Vogel, CG. Parkin, W Koehler, I Vesper, B Petersen, MA. Schweitzer, and RS. Wagner. Use of an insulin bolus advisor facilitates earlier and more frequent changes in insulin therapy parameters in suboptimally controlled patients with diabetes treated with multiple daily insulin injection therapy: results of the ABACUS trial. *Diabetes Technol Ther* 16 (5):310-316, 2014.	Wrong outcomes: not those pre-specified in our protocol. ABACUS Study results from relevant outcomes, has already been publsied (ZIEGLER 2013) and has been included in our review (pre-reruns).
COLIN 2013 I. M. Colin and I. Paris. Glucose meters with built-in automated bolus calculator: Gadget or real value for insulin-treated diabetic patients? *Diabetes Ther.* 4 (1):1-11, 2013.	SR – used as source of references.
SCHMIDT 2013 S. Schmidt, M. Meldgaard, N. Serifovski, C. Storm, B. Gade-Rasmussen, and K. Norgaard. Long-term use of an automated bolus calculator in type 1 diabetes. *Diabetes Technol Ther* 15:A90, 2013.	Conference abstract
SCHMIDT 2012 S. Schmidt, M. Meldgaard, N. Serifovski, C. Storm, T. M. Christensen, B. Gade-Rasmussen, and K. Nørgaard. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. *Diabetes care* 35 (5):984-990, 2012.	Already found study in pre-reruns literature. Was included in the evidence review.
SCHWARTZ 2012 F. L. Schwartz, A. Guo, C. R. Marling, and J. H. Shubrook. Analysis of Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in type 1 diabetes mellitus patients treated with multiple daily insulin injections. *J Diabetes Sci Technol* 6 (1):150-152, 2012.	Overview of publ;ished trial (BARNARD 2011 – already have this study in our review)
TEJERA 2014 C. Tejera, F. M. Morales, A. M. Lopez, B. Galvan, E. Delgado, P. Beato, and V. Hernandez. Experience with insulin-bolus calculator in diabetes type 1 patients in treatment on basal-bolus regimen. *Diabetes* 63:A596, 2014.	Conference abstract

K.3.2 SMBG versus CGM

Reference	Reason for exclusion
ABDELGADIR 2006	Wrong comparisons: SMBG vs. SMBG
ADOLFSSON 2008	Not RCT.
AHMANN 2010	Conference abstract
BAILEY 2009	Not RCT
BATTELINO 2008 T. Battelino and J. Bolinder. Clinical use of real-time continuous glucose monitoring. *Curr.Diabetes Rev.* 4 (3):218-222, 2008.	Review. Not available.
BATTELINO 2011	Wrong population: mixed ages children, young people and adults (60% ≥19 years old) with no adult subgroup analysis.
BATTELINO 2011B	Conference abstract
BECK 2009	Post-hoc analysis of the JDRF study (RCT), but results given for the CGM arm only.
BECK 2009	Post-hoc analysis of RCT and only looks at the CGM arm
BECK 2009	Only includes the CGM group (not vs the SMBG)
BECK 2009A	Wrong population: mixed ages children, young people and adults (52% ≥25 years old) with no adult subgroup analysis.
BECK 2010A	Post-hoc analysis of the JDRF study (RCT), but results given for the CGM arm only.
BECK 2012 Beck RW, Calhoun P, Kollman C. Use of continuous glucose monitoring as an outcome measure in clinical trials. Diabetes Technology and Therapeutics. 2012; 14(10):877-882.	Not available. Wrong population: mixed ages children, young people and adults.
BENNION 2002	Wrong comparison: SMBG vs. SMBG using different monitors
BERGENSTAL 2011	Wrong intervention and comparison: MDI vs. pump. Wrong population: all ages.
BERGENSTAL 2011 R. M. Bergenstal, W. V. Tamborlane, A. Ahmann, J. B. Buse, G. Dailey, S. N. Davis, C. Joyce, T. Peoples, B. A. Perkins, J. B. Welsh, S. M. Willi, and M. A. Wood. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N.Engl.J.Med.* 363 (4):311-320, 2010.	Wrong intervention/comparison: different insulin treatment – pump vs. MDI
BERGENSTAL 2012 Bergenstal RM, Bode BW, Tamler R, Trence DL, Stenger P, Schachner HC et al. Advanced meter features improve postprandial and paired self-monitoring of blood glucose in individuals with diabetes: Results of the actions with the	Not available. Wrong comparisons use of meter with basic function vs. use of meter with advanced functions.

Reference	Reason for exclusion
CONTOUR blood glucose meter and behaviors in frequent testers (ACT) study. Diabetes Technology and Therapeutics. 2012; 14(10):851-857.	
BODE 2004A	Wrong intervention: Continuous glucose monitoring device does not provide real-time sensor glucose values, it just provides an alarm at specific Glc levels to give treatment. Also excluded from Cochrane review for this reason.
BODE 2008	Single arm study – not randomised
BODE 2009	Post-hoc analysis of adults in the JDRF study (RCT), but results given for the CGM arm only.
BODE 2010	Abstract
BODE 2010A	Conference abstract
BORG 2010	Not RCT.
BORG 2011	Post-hoc analysis of ADAG study. Wrong outcomes: associations between indices of glycaemia and CVD risk factors.
BOYNE 2003	Not RCT. Wrong outcomes.
CADUFF 2006	Not RCT. Wrong intervention – Glc. monitoring by impedance spectroscopy. Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (66% type 1 diabetes).
CHASE 2010	Wrong population: all ages. Not RCT.
CHETTY 2008	SR/MA 2008: used for references
CONGET 2011A	Protocol for Battelino 2012
COOKE 2009	Wrong population: mixed type 1 diabetes (53%) and type 2 diabetes with no type 1 diabetes subgroup analysis.
COSSON 2009A	GDG does not agree with the duration of intervention. Intervention not in keeping with medical practice (applied for only 48hrs).
CURRIE 2009	SR/MA 2009: used for

Reference	Reason for exclusion
	references
DAVEY 2010	Wrong comparison: CGM with alarm vs. CGM without alarm.
DEBLOCK 2008	Literature review.
DIEM 2004	Not RCT. Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (83% type 1 diabetes).
DUNN 2004	Not RCT.
FABIATO 2009	Review and clinical scenarios
FARMER 2005	Wrong comparison: SMBG with DSN advice vs SMBG with no DSN advice
FIALLO 2005	Wrong population: not adults (ages are 7 to 17 years old)
FLAMM 2003	Technology Evaluation Center (TEC) Assessment/SR
FLOYD 2012 B Floyd, P Chandra, S Hall, C Phillips, E Alema-Mensah, G Strayhorn, EO. Ofili, and GE. Umpierrez. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol* 6 (5):1094-1102, 2012.	Not available. Review.
GANDI 2012	SR/MA 2012: used for references
GARG 2008	Wrong comparison: SMBG vs. SMBG using different monitors (one has guidance software for a PDA).
GINSBERG 2011	Not available at British library.
GOLDEN 2012	SR/MA 2012: used for references
GROSS 2000 Gross TM, Bode BW, Einhorn D *et al*. Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. *Diabetes Technology and Therapeutics* 2000;**2**:49–56.	Included in the original NICE 2004 GL: observational study
GROSS 2002 Gross TM, Ter Veer A. Continuous glucose monitoring in previously unstudied population subgroups. *Diabetes Technology and Therapeutics* 2000;**2**(Suppl 1):S27–34	Included in the original NICE 2004 GL: observational study
GROSSI 2009	Wrong intervention and comparison: alternate daily pre-prandial mmts vs. alternate daily pre- and post-prandial mmts.
GUILLOD 2007	Not RCT.

Reference	Reason for exclusion
HALFORD 2010	Not RCT
HAUPT 2005	Mixed population – type 1 diabetes and type 2 diabetes (% not given) with no type 1 diabetes subgroup analysis
HEALTH 2011A	Systematic review/Canadian HTA
HERMANIDES 2011	Wrong intervention/comparison. Pump vs. MDIs
HERMANNS 2009	Not addressing review question.
HIRSCH 2009	Literature review.
HOEKS 2011	Review. used for references
HOEKS 2011	Narrative review – used for references
HOIHANSEN 2005	Not an RCT. Only looks at CGM, does not compare with SMBG.
HOIHANSEN 2005	Not RCT. Only CGM used, no SMBG comparison
HUANG 2012	Cost effectiveness and not clinical effectiveness data
JACOBS 2010	Not RCT.
JOHANSEN 2012	Not RCT.
KAPITZA 2003	Not RCT
KEENAN 2012	Not RCT. Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (mainly type 1 diabetes).
KLONOFF 2011	Clinical practice guideline – used for references
KOHUT 2010	Conference abstract
KORDONOURI 2012	Wrong population: children
KOVATCHECV 2008	Not RCT.
KOVATCHEV 2009	Not RCT.
KRISTENSEN 2004	Technical brief. Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (%type 1 diabetes not given).
KUBIAK 2006	Not RCT
LAFFELL 2007	Wrong comparison: paper vs. electronic logbooks using blood glucose meter in both arms.

Reference	Reason for exclusion
LANGELAND 2012	Duration of outcomes not enough to show clinical difference (as agreed by the GDG)
LARBIG 2003	Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (8.2% type 1 diabetes).
LEAL 2010	Not RCT.
LEE 2007	Wrong comparisons: CGM vs SMBG but different insulin treatment in each arm - CSII vs. MDI
LENTERS 2008	Wrong population: mixed population of type 1 diabetes, type 2 diabetes and healthy people with no type 1 diabetes subgroup analysis.
LOGTENBEG 2009	Wrong comparisons – CGM blinded vs. CGM open
LUDWIGSEIBOLD 2012	Not RCT
MARAN 2002 Maran A, Crepaldi C, Tiengo A *et al*. Continuous subcutaneous glucose monitoring in diabetic patients: a multicenter analysis. *Diabetes Care* 2002;**25**:347–52.	Included in the original NICE 2004 GL: observational study
MASTROTOTARO 2008	Not RCT
MORROW 2011	Not RCT.
MUCHMORE 2011	Wrong comparisons: CGM vs SMBG but different insulin treatment in each arm – randomised to different prandial insulins.
NIELSEN 2007	Not RCT.
PATY 2012	Commentary on an RCT. Mixed population of children and adults.
PETROVSKI 2004	Not RCT.
PEYROT 2009	Wrong comparisons: CGM vs SMBG but different insulin treatment in each arm - CSII vs. MDI
PFUTZNER 2012	Not RCT. Accuracy study. Mixed population – type 1 diabetes and type 2 diabetes (50%) with no type 1 diabetes subgroup analysis
PICKUP 2011C	Wrong comparisons – CSII vs. MDI
POHAR 2007	Review. used for references

Reference	Reason for exclusion
POHAR 2007	Review
RIVELINE 2012	Not specified population. Study population includes children with no sub-group analysis carried out.
RUBIN 2009	Not RCT.
RUBIN 2012	Wrong comparisons: CGM vs SMBG but different insulin treatment in each arm - CSII vs. MDI
RUEDY 2012	Narrative review. Primary studies already included in the review.
RYAN 2009	Not RCT.
SZYPOWSKA 2012	SR/MA 2012: used for references
TAMBOURLANE 2008B	JDEF study – wrong population – all ages.
VAZEOU 2011	Literature Review
WILHELM 2006 B. Wilhelm, S. Forst, M. M. Weber, M. Larbig, A. Pfutzner, and T. Forst. Evaluation of CGMS during rapid blood glucose changes in patients with type 1 diabetes. *Diabetes Technol.Ther.* 8 (2):146-155, 2006.	Wrong comparison: SC insulin vs. IV insulin then measured with CGMS and SMBG.
WILSON 2011A	JDRF study results. Wrong outcome: relationship between HbA1c and CGM measurements. Wrong population: all ages.
WOJCIEHOWSKI 2011	SR/MA 2011: used for references
WOLFSDORF 2009	Commentary ON THE JDRF study
WONSTEIN 2007	Not RCT.
YEH 2012	SR/MA 2012: used for references
YOGEV 2003	Wrong population: pregnant women (excluded in Scope).
ZHOU 2012	Not RCT. Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis (mainly type 2 diabetes).
BAY 2013 C Bay, P Kristensen, U Pedersen-Bjergaard, L Tarnow, and B Thorsteinsson. Nocturnal continuous glucose monitoring: accuracy and reliability of hypoglycemia detection in patients with type 1 diabetes at high risk of severe hypoglycemia. *Diabetes Technol.Ther.* 15 (5):371-377, 2013.	Wrong outcomes: CGM in both groups, but assesses usefulness of CGM data.
FRIEDMAN 2013	Survey results (follow-up of

Reference	Reason for exclusion
K Friedman, Jeannette Noyes, and Christopher G. Parkin. 2-Year follow-up to STeP trial shows sustainability of structured self-monitoring of blood glucose utilization: results from the STeP practice logistics and usability survey (STeP PLUS). *Diabetes Technol.Ther.* 15 (4):344-347, 2013.	RCT); does not give RCT data itself. The RCT is in wrong population: type 2 diabetes.
FLOYD 2012A B. Floyd, P. Chandra, S. Hall, C. Phillips, E. Alema-Mensah, G. Strayhorn, E. O. Ofili, and G. E. Umpierrez. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol* 6 (5):1094-1102, 2012.	SR – used as source of references.
GIVEN 2013 J. E. Given, M. J. O'Kane, B. P. Bunting, and V. E. Coates. Comparing patient-generated blood glucose diary records with meter memory in diabetes: a systematic review. *Diabet.Med.* 30 (8):901-913, 2013.	Review of observational studies, not RCTs.
LUIJF 2013 YM. Luijf, JK. Mader, W Doll, T Pieber, A Farret, et al. and AP@home consortium. Accuracy and reliability of continuous glucose monitoring systems: a head-to-head comparison. *Diabetes Technol.Ther.* 15 (8):722-727, 2013.	Wrong outcomes: not clinical outcomes, but performance accuracy and longevity of the sensors.
MORENO 2013 J Moreno-Fernandez, F J Gomez, M Gazquez, M Pedroche, A Garcia-Manzanares, Jose Maria Tenias, Pedro Benito, and Ines Rosa Gomez. Real-time continuous glucose monitoring or continuous subcutaneous insulin infusion, what goes first?: results of a pilot study. *Diabetes Technol.Ther.* 15 (7):596-600, 2013.	Wrong comparison: CGM before CSII vs, CGM after CSII.
PLACE 2013 J Place, A Robert, NB Brahim, P Keith-Hynes, A Farret, MJ Pelletier, B Buckingham, M Breton, B Kovatchev, and E Renard. DiAs web monitoring: a real-time remote monitoring system designed for artificial pancreas outpatient trials. *J Diabetes Sci Technol* 7 (6):1427-1435, 2013.	Testing study of a new technology; not an RCT.
SARTORE 2012 G. Sartore, N. C. Chilelli, S. Burlina, P. D. Stefano, F. Piarulli, D. Fedele, A. Mosca, and A. Lapolla. The importance of HbA1c and glucose variability in patients with type 1 and type 2 diabetes: Outcome of continuous glucose monitoring (CGM). *Acta Diabetol.* 49 (1 Suppl):S153-S160, 2012.	Does not answer the question: just shows correlations of HbA1c with different measures of glucose.
LITTLE 2012 S Little, T Chadwick, P Choudhary, C Brennand, J Stickland, S Barendse., et al. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC Endocr.Disord.* 12:33, 2012.	Study protocol, not results. Study now published (LITTLE 2014) and has been included in our review.
SZYPOWSKA 2012 A. Szypowska, A. Ramotowska, K. Dzygalo, and D. Golicki. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized	SR and MA – used as source of references. We had already included or excluded all the refs in review.

Reference	Reason for exclusion
trials. *EUR.J.ENDOCRINOL.* 166:567-574, 2012.	
AGESEN 2013 R. M. Agesen, P. L. Kristensen, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, P. Hougaard, H.-H. Parving, B. Thorsteinsson, L. Tarnow, and U. Pedersen-Bjergaard. Effect of insulin analogues on frequency of mild hypoglycaemia in patients with type 1 diabetes and recurrent severe hypoglycaemia: The prospective, controlled HypoAna trial. *Diabetologia* 56:S239, 2013.	Conference abstract
BRATINA 2013 N. Bratina. The switch study: The impact of continuous glucose monitoring on health care resource utilization. *Diabetes Technol.Ther.* 15:A3, 2013.	Conference abstract
CHANG 2014A A. Chang, K. Nakamura, T. Bailey, M. Christiansen, N. Bhavaraju, and D. Price. RT-CGM performance ready for independent diabetes management decisions. *Diabetes* 63:A214, 2014.	Conference abstract
CHRISTIANSEN 2013 M Christiansen, T Bailey, E Watkins, David Liljenquist, David Price, Katherine Nakamura, Robert Boock, and Thomas Peyser. A new-generation continuous glucose monitoring system: improved accuracy and reliability compared with a previous-generation system. *Diabetes Technol.Ther.* 15 (10):881-888, 2013.	Not an RCT – observational study.
COKOLIC 2013 M. Cokolic, M. Krajnc, S. Sternad, and M. Rakusa. The use of continuous glucose monitoring device: iPro2 improves long-term management of diabetes mellitus. *Diabetes Technol.Ther.* 15:A57-A58, 2013.	Conference abstract
DIDANGELOS 2014 T. Didangelos, E. Anastasiou, C. Vasilopoulos, C. Zoupas, C. Manes, A. Tsatsoulis, N. Tentolouris, M. Benroubi, E. Pangalos, A. Gerasimidi-Vazeou, and A. Pappas. Improvement of metabolic control after three months of RT-CGM in type 1 diabetics with CSII. the greek multicenter study diamond. *Diabetes Technol.Ther.* 16:A14-A15, 2014.	Conference abstract
FRECKMANN 2013 G. Freckmann, S. Pleus, M. Link, E. Zschornack, H.-M. Klotzer, and C. Haug. Performance evaluation of three continuous glucose monitoring systems: Comparison of six sensors per subject in parallel. *J Diabetes Sci Technol* 7 (4):842-853, 2013.	Not an RCT – observational study.
HERMANNS 2014 N. Hermanns, B. Schumann, B. Kulzer, and T. Haak. The impact of continuous glucose monitoring on low interstitial glucose values and low blood glucose values assessed by point-of-care blood glucose meters: Results of a crossover trial. *J Diabetes Sci Technol* 8 (3):516-522, 2014.	Wrong comparison: CGM (RT) vs. CGM blind (no access to current glucose values and not alerted if critical glucose values reached).
KURU 2014 B. Kuru, M. Sever, E. Aksay, T. Dogan, N. Yalcin, Eren E. Seker, and F. Ustuner. Comparing finger-stick beta-hydroxybutyrate with dipstick urine tests in the	Study ordered for ketones review.

Reference	Reason for exclusion
detection of ketone bodies. *Turk.Acil Tip Derg.* 14 (2):47-52, 2014.	
LINDHOLM 2014 OA. Lindholm, R. Hanas, E. Heintz, S. Jacobson, U. B. Johansson, P. O. Olsson, M. Persson, and S. Werko. CGM and sap are valuable tools in the treatment of diabetes; A swedish health technology assessment. *Diabetes Technol.Ther.* 16:A74, 2014.	Conference abstract
LITTLE 2014 S. A. Little, L. Leelarathna, E. Walkinshaw, H. K. Tan, O. Chapple, A. Lubina-Solomon, T. J. Chadwick, S. Barendse, et al. Recovery of Hypoglycemia Awareness in Long-Standing Type 1 Diabetes: A Multicenter 2 x 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-Monitoring (HypoCOMPaSS). LID - DC_140030 [pii]. *Diabetes Care* 37 (81935-5548 (Electronic)):2114-2122, 2014.	Already found study in first rerun literature, and has been include in our review.
MORENO 2013A C. Moreno, L. Barros, C. Baptista, L. Ruas, M. Alves, S. Gouveia, J. Saraiva, D. Guelho, M. Carvalheiro, and F. Carrilho. Importance of retrospective continuous glucose monitoring in poorly controlled diabetic patients: A system that still has clinical usefulness. *Diabetes Technol.Ther.* 15:A67, 2013.	Conference abstract
MURATA 2014 T. Murata, H. Okada, J. Kishi, K. Yamada, and N. Sakane. The association between the frequency of smbg assessed by data management software and the glycaemic control in T1DM patients. *Diabetes Technol.Ther.* 16:A57, 2014.	Conference abstract
PAPPAS 2013 A. C. Pappas, E. Anastasiou, C. Vasilopoulos, C. Zoupas, C. Manes, A. Tsatsoulis, N. Tentolouris, M. Benroubi, E. Pangalos, A. Gerasimidi-Vazeou, and T. Didangelos. Improvement of metabolic control after three months use of RT-CGM in type 1 diabetics treated with insulin pump: The multicentre Greek DIAMOND study. *Diabetologia* 56:S441, 2013.	Conference abstract
PETROVSKI 2013 G. Petrovski, T. Milenkovic, B. Jovanovska, I. Ahmeti, and I. Bitovska. Intermittent glucose monitoring in type 1 diabetics on insulin pump: Is there difference in glycaemic control between real-time and retrospective analysis? *Diabetologia* 56:S442, 2013.	Conference abstract
PLEUS 2013 S. Pleus, C. Schmid, A. Westhoff, D. Zech, P. Wintergerst, M. Muller, O. Mast, M. Link, E. Stolberg, G. Freckmann, and C. Haug. Comparative handling evaluation of the 1st and 2nd generation of an integrated SMBG system. *Diabetes Technol.Ther.* 15:A70, 2013.	Conference abstract
POOLSUP 2013 N Poolsup, N Suksomboon, and AM Kyaw. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on	SR – used as source of refernces. Not include correct population – type 2 diabetes adults and only

Reference	Reason for exclusion
glucose control in diabetes. *Diabetol Metab Syndr* 5:39, 2013.	type 1 diabetes children studies, not type 1 diabetes adults.
SEQUEIRA 2013 PA. Sequeira, L Montoya, V Ruelas, D Xing, V Chen, R Beck, and AL. Peters. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. *Diabetes Technol.Ther.* 15 (10):855-858, 2013.	Already have this study - Ordered pre-reruns.
VALLEJOMORA 2014 M. R. Vallejo Mora, M. Carreira, Lopez M. Dominguez, M. S. Ruiz De Adana Navas, F. Linares, Rodriguez N. Colomo, et al. Assessment of the usefulness of the bolus calculator in type 1 diabetic patients treated with multiple daily injections. preliminary results. *Diabetes Technol.Ther.* 16:A122, 2014.	Conference abstract
FLOYD 2012 B. Floyd, P. Chandra, S. Hall, C. Phillips, E. Alema-Mensah, G. Strayhorn, E. O. Ofili, and G. E. Umpierrez. Comparative analysis of the efficacy of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes mellitus. *J Diabetes Sci Technol* 6 (5):1094-1102, 2012.	Found by cross-referencing. SR/MA and used as source of references. Already have this study - Ordered pre-reruns.
JENSEN 2014 M. H. Jensen, Z. Mahmoudi, T. F. Christensen, L. Tarnow, E. Seto, M. D. Johansen, and O. K. Hejlesen. Evaluation of an algorithm for retrospective hypoglycemia detection using professional continuous glucose monitoring data. *J.Diabetes Sci.Technol.* 8 (1):117-122, 2014.	Not an RCT.
JENSEN 2013 M. H. Jensen, T. F. Christensen, L. Tarnow, Z. Mahmoudi, M. D. Johansen, and O. K. Hejlesen. Professional continuous glucose monitoring in subjects with type 1 diabetes: Retrospective hypoglycemia detection. *J.Diabetes Sci.Technol.* 7 (1):135-143, 2013.	Not an RCT.

K.4 Insulin therapy

K.4.1 Rapid-acting insulin

Reference	Reason for exclusion
IWAMOTO 2011 Y. Iwamoto, Y. Akanuma, H. Niimi, N. Sasaki, N. Tajima, and R. Kawamori. Comparison between insulin aspart and soluble human insulin in type 1 diabetes (IDDM) patients treated with basal-bolus insulin therapy - Phase III clinical trial in Japan. *Journal of the Japan Diabetes Society* 44 (10):799-811, 2001.	In Japanese.
AMPUDIA-BLASCO 2005	Abstract only.
AVENTIS 2006	Need to contact Aventis or this
ZINMAN 1997 B. Zinman, H. Tildesley, J. L. Chiasson, E. Tsui, and T. Strack. Insulin lispro in	Wrong intervention: insulin delivered by pumps. Also

Reference	Reason for exclusion
CSII: results of a double-blind crossover study. *Diabetes* 46 (3):440-443, 1997.	the basal insulin used is not specified.
HOOGMA 2006 R. P. Hoogma and D. Schumicki. Safety of insulin glulisine when given by continuous subcutaneous infusion using an external pump in patients with type 1 diabetes. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme* 38 (6):429-433, 2006.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified.
SKRHA 2002 J. Skrha, A. Smahelova, M. Andel, M. Vrtovec, J. Subic, A. Kreze, J. Vozar, M. Korecova, V. de Verga, J. Wyatt, S. Metcalfe, and S. Ristic. Insulin lispro improves postprandial glucose control in patients with diabetes mellitus. *Sb Lek* 103 (1):15-21, 2002.	Mixed population of type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis. (Lispro = NOPH vs. Human + NPH)
COLOMBEL 1999 A. Colombel, A. Murat, M. Krempf, B. Kuchly-Anton, and B. Charbonnel. Improvement of blood glucose control in Type 1 diabetic patients treated with lispro and multiple NPH injections. *Diabetic medicine : a journal of the British Diabetic Association* 16 (4):319-324, 1999.	Unclear age-range (N=25; Lispro + NPH vs. Humulin + NPH).
PROVENZANO 2001 C. Provenzano, R. Vero, A. Oliva, G. Leto, L. Puccio, E. Vecci, P. L. Mattioli, and U. Di Mario. Lispro insulin in type 1 diabetic patients on a Mediterranean or normal diet: a randomized, cross-over comparative study with regular insulin. *Diabetes Nutr Metab* 14 (3):133-139, 2001.	Wrong population: mixed ages: 14-44 years.
RASKIN 2001 P. Raskin, J. H. Holcombe, W. V. Tamborlane, J. I. Malone, S. Strowig, J. A. Ahern, and F. Lavent. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. *J.Diabetes Complications* 15 (6):295-300, 2001.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified. Wrong population: adults and young people.
JACOBS 1997 M. A. Jacobs, E. T. Keulen, K. Kanc, S. Casteleijn, P. Scheffer, W. Deville, and R. J. Heine. Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care* 20 (8):1279-1286, 1997.	Wrong population: mixed ages – children and adults.
ALTUNTAS 2003 Y. Altuntas, B. Ozen, B. Ozturk, A. Sengul, S. Ucak, O. Ersoy, and S. Karul. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. *Diabestes Obes.Metab.* 5 (6):371-378, 2003.	Wrong population: type 2 diabetes
KOTSANOS 1997 J. G. Kotsanos, L. Vignati, W. Huster, C. Andrejasich, M. B. Boggs, A. M. Jacobson, D. Marrero, S. D. Mathias, D. Patrick, S. Zalani, and J. Anderson. Health-related quality-of-life results from multinational clinical trials of insulin lispro. Assessing benefits of a new diabetes therapy. *Diabetes Care* 20 (6):948-958, 1997.	Report of 2 x RCTs (Anderson 1997A?? and Anderson 1997B??) that have already been looked at for this Rv.

Reference	Reason for exclusion
ANDERSON 1997 Jr Anderson, R. L. Brunelle, M. E. Trautmann, L. Vignati, R. DiMarchi, D. P. Cameron, D. K. Yeu, P. Zimmet, J. P. Lauvaux, L. F. Van Gaal, J. L. Chiasson, I. M. Fettes, M. H. Tan, et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clin.Ther.* 19 (1):62-72, 1997.	Wrong population: mixed ages of children, young people and adults. No adult subgroup analysis.
HEDMAN 2001 C. A. Hedman, A. C. Orre-Pettersson, T. Lindstrom, and H. J. Arnqvist. Treatment with insulin lispro changes the insulin profile but does not affect the plasma concentrations of IGF-I and IGFBP-1 in type 1 diabetes. *Clin Endocrinol (Oxf)* 55 (1):107-112, 2001.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified.
JOHANSSON 2000 U. B. Johansson, U. C. Adamson, P. E. Lins, and R. A. Wredling. Improved blood glucose variability, HbA1c insuman Infusat and less insulin requirement in IDDM patients using insulin lispro in CSII. The Swedish Multicenter Lispro Insulin Study. *Diabetes Metab.* 26 (3):192-196, 2000.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified.
SCHMAUSS 1998 S. Schmauss, A. Konig, and R. Landgraf. Human insulin analogue [LYS(B28), PRO(B29)]: the ideal pump insulin? *Diabet.Med.* 15 (3):247-249, 1998.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified.
KITABCHI 2012 AE. Kitabchi and AR. Gosmanov. Safety of rapid-acting insulin analogs versus regular human insulin. *Am.J.Med.Sci.* 344 (2):136-141, 2012.	SR – used as source of references.
HOME 2012B P. D. Home. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabestes Obes.Metab.* 14 (9):780-788, 2012.	SR – used as source of references.
ROACH 2004 P. Roach, S. Bai, B. Charbonnel, A. Consoli, C. Taboga, A. Tiengo, and G. Bolli. Effects of multiple daily injection therapy with Humalog mixtures versus separately injected insulin lispro and NPH insulin in adults with type I diabetes mellitus. *Clin.Ther.* 26 (4):502-510, 2004.	Wrong intervention: pre-mixed insulin (this will be covered in a separate Rv question).
ASHWELL 2008 S. G. Ashwell, C. Bradley, J. W. Stephens, E. Witthaus, and P. D. Home. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. *Diabetes Care* 31 (6):1112-1117, 2008.	Wrong intervention: different LA insulin in each group
CHEN 2005 J. W. Chen, T. Lauritzen, J. J. Christiansen, L. H. Jensen, W. H. Clausen, and J. S. Christiansen. Pharmacokinetic profiles of biphasic insulin aspart 30/70 and 70/30 in patients with Type 1 diabetes: a randomized double-blinded crossover study. *Diabet.Med.* 22 (3):273-277, 2005.	Wrong follow-up time: only 15 days treatment

Reference	Reason for exclusion
BARTOLI 2008 P. D. Bartolo, F. Pellicano, A. Scaramuzza, C. Sardu, T. Casetti, E. Bosi, V. Miselli, S. Brandolini, T. Fabbri, P. Meandri, and F. Cannatà. Better postprandial glucose stability during continuous subcutaneous infusion with insulin aspart compared with insulin lispro in patients with type 1 diabetes. *Diabetes Technol.Ther.* 10 (6):495-498, 2008.	Wrong follow-up time: only 3 days
LINDSTROM 2002 T. Lindstrom, C. A. Hedman, and H. J. Arnqvist. Use of a novel double-antibody technique to describe the pharmacokinetics of rapid-acting insulin analogs. *Diabetes Care* 25 (6):1049-1054, 2002.	Wrong follow-up time: only 13 hour treatment
THORISDOTTIR 2009 R. L. Thorisdottir, T. Parkner, J. W. Chen, N. Ejskjaer, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of biphasic insulin aspart 30, 50, 70 and pure insulin aspart: a randomized, quadruple crossover study. *Basic Clin.Pharmacol.Toxicol.* 104 (3):216-221, 2009.	Wrong follow-up time: only 800 minutess.
PLANK 2002 J. Plank, A. Wutte, G. Brunner, A. Siebenhofer, B. Semlitsch, R. Sommer, S. Hirschberger, and T. R. Pieber. A direct comparison of insulin aspart and insulin lispro in patients with type 1 diabetes. *Diabetes Care* 25 (11):2053-2057, 2002.	Wrong follow-up time: only 6 hours treatment
RAVE 2006 K. Rave, O. Klein, A. D. Frick, and R. H. Becker. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. *Diabetes Care* 29 (8):1812-1817, 2006.	Wrong follow-up time: only 6 hours treatment
MA 2012A Z. Ma, T. Parkner, J. Frystyk, T. Laursen, T. Lauritzen, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: A randomized, quadruple crossover study. *Diabetes Technol.Ther.* 14 (7):589-595, 2012.	Wrong follow-up time: only 720 hours
PETTIS 2011B R. J. Pettis, L. Hirsch, C. Kapitza, L. Nosek, U. Hövelmann, H. J. Kurth, D. E. Sutter, N. G. Harvey, and L. Heinemann. Microneedle-based intradermal versus subcutaneous administration of regular human insulin or insulin lispro: pharmacokinetics and postprandial glycemic excursions in patients with type 1 diabetes. *Diabetes Technol.Ther.* 13 (4):443-450, 2011.	Wrong follow-up time: only 5 days treatment
HEISE 2008 T. Heise, U. Eckers, K. Kanc, J. N. Nielsen, and L. Nosek. The pharmacokinetic and pharmacodynamic properties of different formulations of biphasic insulin aspart: a randomized, glucose clamp, crossover study. *Diabetes Technol.Ther.* 10 (6):479-485, 2008.	Wrong follow-up time: only 28 hours
UMPIERREZ 2009 G. E. Umpierrez, S. Jones, D. Smiley, P. Mulligan, T. Keyler, A. Temponi, C.	Wrong population: age unclear, and mixed

Reference	Reason for exclusion
Semakula, D. Umpierrez, L. Peng, M. CerÃ³n, and G. Robalino. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. *Diabetes Care* 32 (7):1164-1169, 2009.	population (not just diabetes). Authors contacted and informed us that the population was >70% type 1 diabetes. However, this study was agreed by the GDG to be excluded because it is DKA patients, and management of DKA is outside of the guideline scope.
BI 2007 Y. F. Bi, L. B. Zhao, X. Y. Li, W. Q. Wang, S. Y. Sun, Y. H. Chen, J. Hong, T. W. Su, J. M. Liu, and G. Ning. A 2-way cross-over, open-labeled trial to compare efficacy and safety of insulin Aspart and Novolin R delivered with CSII in 21 Chinese diabetic patients. *Chin.Med.J.(Engl).* 120 (19):1700-1703, 2007.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis.
KAMOI 2011 K. Kamoi, Y. Shinozaki, K. Furukawa, and H. Sasaki. Decreased active GLP-1 response following large test meal in patients with type 1 diabetes using bolus insulin analogues. *Endocr.J.* 58 (10):905-911, 2011.	Not an RCT. Age-group unclear.
HEINEMANN 2011 L Heinemann, M Hompesch, F Flacke, P Simms, R Pohl, K Albus, A Pfutzner, and S Steiner. Reduction of postprandial glycemic excursions in patients with type 1 diabetes: a novel human insulin formulation versus a rapid-acting insulin analog and regular human insulin. *J Diabetes Sci Technol* 5 (3):681-686, 2011.	Not an RCT.
GRIFFEN 2006 S. C. Griffen, K. Oostema, K. L. Stanhope, J. Graham, D. M. Styne, N. Glaser, D. E. Cummings, M. H. Connors, and P. J. Havel. Administration of Lispro insulin with meals improves glycemic control, increases circulating leptin, and suppresses ghrelin, compared with regular/NPH insulin in female patients with type 1 diabetes. *J.Clin.Endocrinol.Metab.* 91 (2):485-491, 2006.	Wrong population: mixed ages of children, young people and adults.
ZIEGEKASCH 2009 H.-J. Ziegelasch and A. Thomas. Analogue insulin reduces post-prandial glucose levels. *Diabetes* 58, 2009.	Conference abstract. Already have enough RCT data, and this study uses a mixed population of type 1 diabetes and type 2 diabetes.
SKREKOWSKA BARAN 2004 I. Skrzekowska-Baran, O. Pankiewicz, P. Rys, and M. T. Malecki. A comparison of efficacy and safety of insulin aspart and human insulin in treatment of type 1 diabetes mellitus. The results of a systematic review. *Diabetologia* 52 (S1):S387-S388, 2009.	Conference abstract of an SR.
HELLER 2009C S. Heller, B. W. Bode, P. Kozlovski, and A. Svendsen. Examining the glycaemic and hypoglycaemic benefits with rapid-acting insulin analogues: A meta-analysis of insulin aspart versus regular human insulin in randomised controlled trials. *Diabetologia* 52 (S1):S359-S360, 2009.	Conference abstract of an MA.

Reference	Reason for exclusion
BUSE 2011 J. B. Buse, S. K. Garg, J. S. Skyler, D. E. Vaughn, and D. B. Muchmore. Comparison of human hyaluronidase + Recombinant Human Insulin (RHI) vs. insulin lispro in a basal-bolus regimen in patients with type 1 diabetes (T1DM). *Diabetes* 60:A18-A19, 2011.	Conference abstract. Wrong intervention: human insulin + hyaluronidase.
GAO 2008 Y. Gao, G. Li, Y. Li, X. Guo, G. Yuan, Q. Gong, L. Yan, Y. Zheng, and J. Zhang. Postprandial blood glucose response to a standard test meal in insulin-requiring patients with diabetes treated with insulin lispro mix 50 or human insulin mix 50. *Int.J.Clin.Pract.* 62 (9):1344-1351, 2008.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis. Wrong intervention: mixed insulin.
GARG 2010 S. Garg, F. J. Ampudia-Blasco, and M. Pfohl. Rapid-acting insulin analogues in Basal-bolus regimens in type 1 diabetes mellitus. *Endocr Pract* 16 (3):486-505, 2010.	SR – used as a source of references
HELMS 2009 KL. Helms and KW. Kelley. Insulin glulisine: an evaluation of its pharmacodynamic properties and clinical application. *Ann.Pharmacother.* 43 (4):658-668, 2009.	SR – used as a source of references
RYS 2011 P. Rys, O. Pankiewicz, K. Lach, A. Kwaskowski, I. Skrzekowska-Baran, and M. T. Malecki. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. *Diabetes Metab.* 37 (3):190-200, 2011.	SR – used as a source of references
RECASENS 2003 M. Recasens, E. Aguilera, R. MorÃ-nigo, R. Casamitjana, F. Nicoletti, R. Gomis, and I. Conget. Insulin lispro is as effective as regular insulin in optimising metabolic control and preserving beta-cell function at onset of type 1 diabetes mellitus. *Diabetes Res.Clin.Pract.* 60 (3):153-159, 2003.	Wrong population: age-group unclear
HEINEMANN 2012 L. Heinemann, L. Nosek, F. Flacke, K. Albus, A. Krasner, P. Pichotta, T. Heise, and S. Steiner. U-100, pH-Neutral formulation of VIAject() : faster onset of action than insulin lispro in patients with type 1 diabetes. *Diabestes Obes.Metab.* 14 (3):222-227, 2012.	Wrong population: age-group unclear
FORST 2005 T. Forst, S. Forst, K. Strunk, M. Löbig, K. Welter, C. Kazda, and A. Pfützner. Impact of insulin on microvascular blood flow and endothelial cell function in the postprandial state in patients with Type 1 diabetes. *J.Diabetes Complications* 19 (3):128-132, 2005.	Wrong population: age-group unclear. Also wrong outcomes.
RICHTER 2005 B. Richter and G. Neises. 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane database of systematic reviews (Online)* (1):CD003816, 2005.	Wrong intervention: animal insulins. We are not going to look at animal insulins as these are rarely used in the

HEINEMANN 2012 L. Heinemann, L. Nosek, F. Flacke, K. Albus, A. Krasner, P. Pichotta, T. Heise, and S. Steiner. U-100, pH-Neutral formulation of VIAject(®) : faster onset of action than insulin lispro in patients with type 1 diabetes. *Diabestes Obes.Metab.* 14 (3):222-227, 2012.	Already have this study - ordered pre-reruns and excluded as not licenced drug (Ulimorelin).
Reference	**Reason for exclusion**
	UK any more.
ROACH 2003 P. Roach, J. Woodworth, U. Gudat, B. Cerimele, F. Diebler, M. Pein, and M. Dreyer. A 75% insulin lispro/25% NPL mixture provides a longer duration of insulin activity compared with insulin lispro alone in patients with Type 1 diabetes. *Diabet.Med.* 20 (11):946-952, 2003.	Wrong population: age-group unclear
SIEBENHOFER 2009 A Siebenhofer, J Plank, A Berghold, K Jeitler, K Horvath, M Narath, R Gfrerer, and TR. Pieber. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev* Issue 2:CD003287, 2006.	Cochrane review – used as source of references.
CHEN 2006 J. W. Chen, T. Lauritzen, A. Bojesen, and J. S. Christiansen. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. *Diabestes Obes.Metab.* 8 (6):682-689, 2006.	Wrong intervention: biphasic Aspart (Novomix 30). Mixed insulins will be covered in a separate Rv.
DEL SINDACO 1998 (ID 297) P. Del Sindaco, M. Ciofetta, C. Lalli, G. Perriello, S. Pampanelli, E. Torlone, P. Brunetti, and G. B. Bolli. Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. *Diabet.Med.* 15:592-600, 1998.	Basal regimens not standardised for clinical practice.
DEVRIES 2003 J. H. DeVries, A. Lindholm, J. L. Jacobsen, R. J. Heine, and P. D. Home. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. *Diabet.Med.* 20 (4):312-318, 2003.	The LA insulin has been given using different doses in each arm.
GABRY 2004 K. E. Gabry. Clinical review: NDA 21,629 (Insulin glulisine). Anonymous. Anonymous. Silver Spring, USA:Center for Drug Evaluation and Research (CDER). 2004.	Data for the relevant RCT in this report has subsequently been published (Dreyer 2005A)
BAY 2013 C. Bay, Kristensen P. Lommer, U. Pedersen-Bjergaard, L. Tarnow, and B. Thorsteinsson. Nocturnal hypoglycaemia: Effect of insulin analogues compared to human insulin in type 1 diabetic patients prone to severe hypoglycaemia. *Diabetologia* 56:S239, 2013.	Conference abstract
MA 2012A Z. Ma, T. Parkner, J. Frystyk, T. Laursen, T. Lauritzen, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: a	Already have this study - Ordered pre-reruns.

randomized, quadruple crossover study. *Diabetes Technol.Ther.* 14 (7):589-595, 2012.	
MA 2014 Z Ma, Jens Sandahl Christiansen, Torben Laursen, Chunsen Wu, Torsten Lauritzen, Tina Parkner, and Jan Frystyk. Effects of human insulin and insulin aspart preparations on levels of IGF-I, IGFBPs and IGF bioactivity in patients with type 1 diabetes. *BMC Endocr Disord* 14 (1):35, 2014.	Wrong outcomes: not those specified in our protocol. And also short follow-up (only 9 hours)
Additional studies from old GL, TA and cross-referencing SRs, MAs and other GLs	
ZINMAN 1999 (176) B. Zinman, S. Ross, R. V. Campos, and T. Strack. Effectiveness of human ultralente versus NPH insulin in providing basal insulin replacement for an insulin lispro multiple daily injection regimen: A double-blind randomized prospective trial. *Diabetes Care* 22 (4):603-608, 1999.	Wrong intervention: ultralente (no longer used in UK).
BRUNELLE (44) R. L. Brunelle, J. Llewelyn, J. H. Anderson, Jr., E. A. M. Gale, and V. A. Koivisto. Meta-analysis of the effect of insulin lispro on severe hypoglycemia in patients with type 1 diabetes. *Diabetes Care* 21 (10):1726-1731, 1998.	Meta-analysis – used as source of references.
BAKER 1998 (1017) A. B. Ahmed and P. D. Home. The effect of the insulin analog lispro on nighttime blood glucose control in type 1 diabetic patients. *Diabetes Care* 21 (1):32-37, 1998.	Wrong outcomes: only reports blood glucose.
EBELING 1997 (1032) P. Ebeling, P. A. Jansson, U. Smith, C. Lalli, G. B. Bolli, and V. A. Koivisto. Strategies toward improved control during insulin lispro therapy in IDDM. Importance of basal insulin. *Diabetes Care* 20 (8):1287-1289, 1997.	Not an RCT (no comparison group).
FANELLI 2002 (1019) C. G. Fanelli, S. Pampanelli, F. Porcellati, P. Rossetti, P. Brunetti, and G. B. Bolli. Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. *Ann.Intern.Med.* 136 (137):504-514, 2002.	Wrong treatment regimen: the same rapid acting insulin and LA insulin used in both arms. Once/day vs. once/day at different times (SA + LA before dinner vs. SA at dinner + LA at bedtime).
LINDHOLM 1999 (1065) A. Lindholm, J. McEwen, and A. P. Riis. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. *Diabetes Care* 22 (5):801-805, 1999.	Wrong follow-up time: only 1 day treatment.
HERMANSEN 2001 (1045) K. Hermansen, S. Madsbad, H. Perrild, A. Kristensen, and M. Axelsen. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: A randomized open crossover trial in type 1 diabetic subjects on basal-bolus therapy. *Diabetes Care* 24 (2):296-301, 2001.	Wrong intervention: LA vs. LA insulin
STADES 2002 (1027) A. M. Stades, J. B. Hoekstra, den Tweel van, I, D. W. Erkelens, F. Holleman, and STABILITY Study Group. Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults: a real-life design. *Diabetes Care* 25 (4):712-717, 2002.	Wrong intervention: LA insulin once vs. twice

ROACH (1043) P. Roach, T. Strack, V. Arora, and Z. Zhao. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. *Int.J.Clin.Pract.* 55 (3):177-182, 2001.	Wrong intervention: mixed insulin. This will be covered in a separate Rv.
DUNBAR 1994 (1054) J. M. Dunbar, P. M. Madden, D. T. Gleeson, T. M. Fiad, and T. J. McKenna. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. *Diabetes Care* 17 (8):874-878, 1994.	Wrong intervention: mixed insulins
ROACH 1999 (1029) P. Roach, M. Trautmann, V. Arora, B. Sun, and J. H. Anderson, Jr. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. *Clin.Ther.* 21 (3):523-534, 1999.	Wrong intervention: mixed insulins
BODE 2001 B. W. Bode and P. Strange. Efficacy, safety, and pump compatibility of insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. *Diabetes Care* 24 (1):69-72, 2001.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified.
RENNER 1999 (1048) R. Renner, A. Pfutzner, M. Trautmann, O. Harzer, K. Sauter, and R. Landgraf. Use of insulin lispro in continuous subcutaneous insulin infusion treatment: Results of a multicenter trial. *Diabetes Care* 22 (5):784-788, 1999.	Wrong intervention: insulin delivered by pumps. Also the basal insulin used is not specified. Age range also unclear.
DAVEY 1997 (291) P. Davey, D. Grainger, J. MacMillan, N. Rajan, M. Aristides, and M. Gliksman. Clinical outcomes with insulin lispro compared with human regular insulin: A meta-analysis. *Clin.Ther.* 19 (4):656-674, 1997.	MA – used as a source of references.
BODE 2002 B. Bode, R. Weinstein, D. Bell, J. McGill, D. Nadeau, P. Raskin, J. Davidson, R. Henry, W.-C. Huang, and R. R. Reinhardt. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care* 25 (3):439-444, 2002.	Wrong insulin device: pumps
PAMPANELLI 1995 S. Pampanelli, E. Torlone, C. Ialli, P. Del Sindaco, M. Ciofetta, M. Lepore, L. Bartocci, P. Brunetti, and G. B. Bolli. Improved postprandial metabolic control after subcutaneous injection of a short-acting insulin analog in IDDM of short duration with residual pancreatic beta-cell function. *Diabetes Care* 18 (11):1452-1459, 1995.	Not an RCT
HOWEY 1995 D. C. Howey, R. R. Bowsher, R. L. Brunelle, H. M. Rowe, P. F. Santa, J. Downing-Shelton, and J. R. Woodworth. [Lys(B28), Pro(B29)]-human insulin: effect of injection time on postprandial glycemia. *Clin Pharmacol Ther* 58 (4):459-469,	Wrong follow-up time: 5 days treatment

1995.	

K.4.2 Long-acting insulin

Reference	Reason for exclusion
ROACH 2004 P. Roach, S. Bai, B. Charbonnel, A. Consoli, C. Taboga, A. Tiengo, and G. Bolli. Effects of multiple daily injection therapy with Humalog mixtures versus separately injected insulin lispro and NPH insulin in adults with type I diabetes mellitus. *Clin.Ther.* 26 (4):502-510, 2004.	Wrong comparison: The long-acting drug in each arm was the same.
HERZ 2002 M. Herz, V. Arora, B. Sun, S. C. Ferguson, G. B. Bolli, and B. M. Frier. Basal-bolus insulin therapy in Type 1 diabetes: Comparative study of pre-meal administration of a fixed mixture of insulin lispro (50%) and neutral protamine lispro (50%) with human soluble insulin. *Diabet.Med.* 19 (11):917-923, 2002.	Wrong comparison: MIX50 Insulin
TESTA 2012A MA. Testa, J Gill, M Su, RR. Turner, L Blonde, and DC. Simonson. Comparative Effectiveness of Basal-Bolus Versus Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and Type 2 Diabetes: A Randomized, Controlled, Crossover Trial. *J.Clin.Endocrinol.Metab.* 97 (10):3504-3514, 2012.	Wrong comparison: Pre-mix Insulin
MONAMI 2009 M. Monami, N. Marchionni, and E. Mannucci. Long-acting insulin analogues NPH human insulin in type 1 diabetes: a meta-analysis. *Diabetes Obesity and Metabolism* 11 (4):372-378, 2009.	Meta-analysis: used for references
FELEDER 2012 E. C. Feleder, G. A. Yerino, E. K. Halabe, J. L. Tombazzi, and J. M. Farias. Phase IV study comparing diurnal glycemic profile following the administration of 2 NPH plus regular human DNA recombinant insulin regimens in type 1 diabetes mellitus (T1DM) adult patients. *Arzneim.-Forsch.Drug Res.* 62 (6):267-273, 2012.	Wrong comparison: NPH vs NPH and outcomes only at 12 hours post-treatment
TOKUBUCHI 2010 I. Tokubuchi, K. Muraishi, S. Sato, T. Kato, K. Hara, K. Tanaka, H. Kaku, Y. Tajiri, and K. Yamada. Distinct pharmacodynamics of insulin glargine and insulin detemir: Crossover comparison in Type 1 and Type 2 diabetic patients on basal-bolus regimen. *Diabetes Res.Clin.Pract.* 90 (3):e64-e66, 2010.	Wrong outcomes: blood glucose only
BRADLEY 2007 C. Bradley, R. Plowright, J. Stewart, J. Valentine, and E. Witthaus. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. *Health Qual Life Outcomes* 5:57, 2007.	Data from another trial published pre-2003 (Witthaus 2001)
HOME 2009 P. D. Home and P. Lagarenne. Combined randomised controlled trial experience of malignancies in studies using insulin glargine. *Diabetologia* 52	Review, no meta-analysis.

Reference	Reason for exclusion
(12):2499-2506, 2009.	
WANG 2012 F Wang, J Surh, and M Kaur. Insulin degludec as an ultralong-acting basal insulin once a day: a systematic review. *Diabetes Metab Syndr Obes* 5:191-204, 2012.	SR with no meta-analysis Degludec-Aspart
KRISTENSEN 2012 P. L. Kristensen, U. Pedersen-Bjergaard, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, H.-H. Parving, B. Thorsteinsson, and L. Tarnow. A prospective randomised cross-over study of the effect of insulin analogues and human insulin on the frequency of severe hypoglycaemia in patients with type 1 diabetes and recurrent hypoglycaemia (the HypoAna trial): study rationale and design. *BMC Endocr.Disord.* 12, 2012.	Study rationale and design – no results. Detemir-Aspart
SZYPOWSKA 2011A A. Szypowska, D. Golicki, L. Groele, and E. Pankowska. Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. *Polskie Archiwum Medycyny Wewnetrznej* 121 (7-8):237-246, 2011.	SR and meta-analysis but all ages mixed.
SINGH 2009 S. R. Singh, F. Ahmad, A. Lal, C. Yu, Z. Bai, and H. B. Bpharm. Efficacy and safety of insulin analogues for the management of diabetes mellitus: A meta-analysis. *Can.Med.Assoc.J.* 180 (4):385-397, 2009.	Meta-analysis: used for references
THALANGE 2010 N. Thalange, A. Bereket, J. Larsen, L. C. Hiort, and V. Peterkova. Development of insulin detemir/insulin aspart crossreacting antibodies following treatment with insulin detemir in type 1 diabetes patients over 104 weeks. *Pediatr.Diabetes* 11:83, 2010.	Conference abstract Detemir-Aspart
NEMETHYOVA 2009 Z. Nemethyova, Z. Schroner, and V. Uliciansky. Effect of basal insulin detemir on weight and hypoglycemia in T1DM and T2DM. *Diabetes* 58, 2009.	Conference abstract (not of an RCT) Detemir-Aspart
SZYPOWSKA 2009 A. Szypowska, D. Golicki, L. Groele, and E. Pankowska. Better metabolic control, less hypoglycaemia and less weight gain with insulin detemir versus NPH insulin in intensive insulin therapy for patients with type 1 diabetes. A meta-analysis. *Diabetologia* 52 (S1):S387, 2009.	Conference abstract: already have enough published RCT data for this comparison (detemir vs. NPH)
HERMANSEN 2009B K. Hermansen, S. Heller, M. Andersen, and D. L. Russell-Jones. Lower rate of hypoglycaemia but comparable glycaemic control with insulin detemir compared to NPH insulin in patients with type l diabetes. *Diabetologia* 52 (S1):S359, 2009.	Conference abstract: already have enough published RCT data for this comparison (detemir vs. NPH)
PIEBER 2007 T. R. Pieber, H. C. Treichel, B. Hompesch, A. Philotheou, L. Mordhorst, M. A. Gall, and L. I. Robertson. Comparison of insulin detemir and insulin glargine in	Conference abstract: degludec vs. glargine but only 5 days treatment

Reference	Reason for exclusion
subjects with Type 1 diabetes using intensive insulin therapy. *Diabet.Med.* 24 (6):635-642, 2007.	
HOME 2011A P. D. Home, L. Meneghini, R. E. Ratner, T. Johansen, T. E. Christensen, J. Jendle, A. P. Roberts, J. H. DeVries, and K. I. Birkeland. A comparison of quality of life measured with the SF-36 for insulin degludec and insulin glargine in people with type 1 diabetes. *Diabetologia* 54:S384, 2011.	Conference abstract: trial has now been fully published and has been included in our review.
HIRSCH 2011A I. Hirsch, E. Franek, J. P. Courreges, H. Mersebach, P. Dykiel, and B. W. Bode. IDegAsp, a soluble insulin combination of ultra-long-acting insulin degludec and insulin aspart, used once daily in basal-bolus treatment with insulin aspart in type 1 diabetes. *Diabetologia* 54:S427, 2011.	Conference abstract – wrong intervention: mixed insulin (covered in another review question in this guideline). Now published as a full paper (HIRSCH 2012B)
HELLER 2011A S. R. Heller, T. Pieber, S. Korsatko, G. Kohler, S. Deller, G. Bock, S. Zahiragic, J. Mader, C. Roepstorff, S. Rasmussen, and H. Haahr. A higher counter-regulatory hormone response is seen with insulin degludec than insulin glargine in response to induced hypoglycaemia in type 1 diabetes. *Diabetologia* 54:S261, 2011.	Conference abstract: degludec vs. glargine but only 5 days treatment
HELLER 2012A S. Heller, A. M. O. Francisco, H. Pei, and D. Russell-Jones. Basal-bolus therapy with insulin degludec improves long-term glycaemic control with less nocturnal hypoglycaemia compared with insulin glargine in Type 1 diabetes: Results of a one year trial. *Diabet.Med.* 29:23-24, 2012.	Conference abstract: trial has now been fully published and has been included in our review.
HELLER 2011 S. Heller, A. M. Francisc, H. Pei, and D. Russelljones. Insulin degludec improves long-term glycemic control with less nocturnal hypoglycemia compared with insulin glargine: 1-year results from a randomized basal-bolus trial in type 1 diabetes. *Diabetes* 60:A19, 2011.	Conference abstract: trial has now been fully published and has been included in our review.
HEISE 2011A T. Heise, U. Hovelmann, L. Nosek, S. G. Bottcher, C. Granhall, and H. Haahr. Insulin degludec: Two-fold longer half-life and a more consistent pharmacokinetic profile than insulin glargine. *Diabetologia* 54:S425, 2011.	Conference abstract: degludec vs. glargine but only 8 days treatment
HEISE 2010 T. Heise, L. Hermanski, L. Nosek, A. Feldmann, S. Rasmussen, T. K. Stryhn, and H. Haahr. Insulin degludec: Less pharmacodynamic variability than insulin glargine under steady state conditions. *Diabetologia* 53:S387, 2010.	Conference abstract: degludec vs. glargine but only 12 days treatment
GOUGH 2012 S. C. L. Gough, R. Ratner, C. Mathieu, Prato S. Del, B. Bode, H. Mersebach, L. Endahl, and B. Zinman. Prospectively planned meta-analysis comparing hypoglycaemia rates of insulin degludec with those of insulin glargine in all patients and an elderly (>=65 year) subgroup. *Diabetologia* 55:S253-S254, 2012.	Conference abstract: degludec vs. glargine but sub-analysis of previous trials in older people

Reference	Reason for exclusion
GARIMELLA 2011A M. Garimella, S. Mitchell, and M. Burge. Does caloric intake explain the weight-neutral effects of insulin detemir versus insulin glargine in type 1 diabetes? *J.Investig.Med.* 59 (1):119, 2011.	Conference abstract: degludec vs. glargine but only 3 weeks treatment
COOPER 2012 J. G. Cooper, C. Mathieu, P. Hollander, B. Miranda-Palma, E. Franek, S. Bain, J. Larsen, S. C. Tamer, and D. L. Russell-Jones. Insulin degludec allows for flexible daily dosing in type 1 diabetes, providing equal glycaemic control with less nocturnal hypoglycaemia than insulin glargine over 52 weeks. *Diabetologia* 55:S374, 2012.	Conference abstract (RCT in type 1 diabetes adults; degludec vs. glargine; fulfils our inclusion criteria and we need more RCT data on this comparison, so we are contacting authors)
BURGE 2011 M. R. Burge, S. Mitchell, and M. Garimella. Does insulin detemir alter satiety or caloric intake to control weight? *Diabetologia* 54:S426, 2011.	Conference abstract: degludec vs. glargine but only 3 weeks treatment
BLEVINS 2012 T. Blevins, J. Rosenstock, R. M. Bergenstal, L. A. Morrow, M. J. Prince, Y. Qu, V. P. Sinha, D. C. Howey, and S. J. Jacober. Better glycaemic control and weight loss with the novel long-acting PEGylated basal insulin LY2605541 compared with insulin glargine in patients with type 1 diabetes. *Diabetologia* 55:S377, 2012.	Conference abstract: wrong treatment – PEGylated insulin lispro
ANDERSON 2012 E. J. Anderson, C. Stevens, E. Cagliero, H. Zheng, H. Lee, and D. M. Nathan. Dawn revisited: Does NPH insulin treatment reduce glycemia more than lantus? *Diabetes* 61:A598-A599, 2012.	Conference abstract: already have enough published RCT data for this comparison (NPH vs. glargine)
ASHWELL 2006 S. G. Ashwell, S. A. Amiel, R. W. Bilous, U. Dashora, S. R. Heller, D. A. Hepburn, S. D. Shutler, J. W. Stephens, and P. D. Home. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes. *Diabet.Med.* 23 (3):285-292, 2006.	Glargine vs. NPH but a different meal-time insulin given in each arm, thus not a true comparison of Glargine vs. NPH
CHARCA 2010 A. R. Chacra, M. Kipnes, L. L. Ilag, S. Sarwat, J. Giaconia, and J. Chan. Comparison of insulin lispro protamine suspension and insulin detemir in basal-bolus therapy in patients with Type 1 diabetes. *Diabet.Med.* 27 (5):563-569, 2010.	Wrong comparison: long vs. rapid acting (lispro-proatmine)
GERICH 2006 J. Gerich, R. H. A. Becker, R. Zhu, and G. B. Bolli. Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes Technol Ther* 8 (2):237-243, 2006.	Re-analysis of data from 3 trials. Trials not meet our inclusion criteria (healthy people, not RCT or already included)
JOHANSSON 2007 U. B. Johansson, R. Wredling, U. Adamson, and P. E. Lins. A morning dose of insulin glargine prevents nocturnal ketosis after postprandial interruption of continuous subcutaneous insulin infusion with insulin lispro. *Diabetes Metab.* 33 (6):469-471, 2007.	Wrong comparison: lispro by CSII vs. partial basal replacement by glargine

Reference	Reason for exclusion
TAMAS 2001 Gy Tamas, M. Marre, R. Astorga, I. Dedov, J. Jacobsen, and A. Lindholm. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. *Diabetes Res.Clin.Pract.* 54 (2):105-114, 2001.	Wrong comparison: rapid (aspart) vs. rapid (human insulin)
GRIFFEN 2006 S. C. Griffen, K. Oostema, K. L. Stanhope, J. Graham, D. M. Styne, N. Glaser, D. E. Cummings, M. H. Connors, and P. J. Havel. Administration of Lispro insulin with meals improves glycemic control, increases circulating leptin, and suppresses ghrelin, compared with regular/NPH insulin in female patients with type 1 diabetes. *J.Clin.Endocrinol.Metab.* 91 (2):485-491, 2006.	Wrong comparison: rapid (Lispro) vs. rapid (human insulin)
GARG 2004 S. K. Garg, J. M. Paul, J. I. Karsten, L. Menditto, and P. A. Gottlieb. Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. *Diabetes Technol Ther* 6 (5):589-595, 2004.	Not an RCT
DOYLE 2004 E. A. Doyle, S. A. Weinzimer, A. T. Steffen, J. A. Ahern, M. Vincent, and W. V. Tamborlane. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care* 27 (7):1554-1558, 2004.	Wrong population: mixed ages 8-21 years.
UMPIERREZ 2009 G. E. Umpierrez, S. Jones, D. Smiley, P. Mulligan, T. Keyler, A. Temponi, C. Semakula, D. Umpierrez, L. Peng, M. CerÃ³n, and G. Robalino. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. *Diabetes Care* 32 (7):1164-1169, 2009.	Wrong population: DKA not type 1 diabetes Authors contacted and informed us that the population was >70% type 1 diabetes. However, this study was agreed by the GDG to be excluded because it is DKA patients, and management of DKA is outside of the guideline scope.
GARG 2010A S. Garg, E. Moser, M.-P. Dain, and A. Rodionova. Clinical experience with insulin glargine in type 1 diabetes. *Diabetes Technol Ther* 12 (11):835-846, 2010.	SR but no meta-analysis
CENGIZ 2012 E. Cengiz, K. L. Swan, W. V. Tamborlane, J. L. Sherr, M. Martin, and S. A. Weinzimer. The alteration of aspart insulin pharmacodynamics when mixed with detemir insulin. *Diabetes Care* 35 (4):690-692, 2012.	Wrong population: young people Detemir-Aspart
ASHWELL 2006B S. G. Ashwell, J. Gebbie, and P. D. Home. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. *Diabet.Med.* 23 (8):879-886, 2006.	Wrong comparison: once vs. twice glargine (another review question will cover this)

Reference	Reason for exclusion
HASSAN 2008 K. Hassan, L. M. Rodriguez, S. E. Johnson, S. Tadlock, and R. A. Heptulla. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. *Pediatrics* 121 (3):e466-e472, 2008.	Wrong population: children
VELASQUEZ 2008 P A. Velasquez-Mieyer and C P. Neira. Biphasic insulin aspart 30 for the treatment of type 1 diabetes mellitus. *Expert Opin Pharmacother* 9 (13):2377-2382, 2008.	Wrong comparison: pre-mix Aspart 30
FLOCH 2009 J. P. Floch, M. Lévy, H. Mosnier-Pudar, F. Nobels, S. Laroche, S. Gonbert, E. Eschwege, and P. Fontaine. Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). *Diabetes Care* 32 (1):32-37, 2009.	Wrong comparison: once vs. twice detemir (another review question will cover this)
DEJGAARD 2009 A. Dejgaard, H. Lynggaard, J. Rastam, and Thomsen M. Krogsgaard. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: A meta-analysis. *Diabetologia* 52 (12):2507-2512, 2009.	Meta-analysis but have pooled trials together which were type 1 diabetes or type 2 diabetes ; no type 1 diabetes subgroup analysis. Used for references.
THOMAS 2007 R. M. Thomas, A. Aldibbiat, W. Griffin, M. A. Cox, N. J. Leech, and J. A. Shaw. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. *Diabet.Med.* 24 (7):778-783, 2007.	Wrong comparisons: glargine vs. CSII vs. education
DEVRIES 2003 J. H. DeVries, A. Lindholm, J. L. Jacobsen, R. J. Heine, and P. D. Home. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with Type 1 diabetes. *Diabet.Med.* 20 (4):312-318, 2003.	Wrong comparison: NPH vs. NPH.
RECASSENS 2003 M. Recasens, E. Aguilera, R. MorÃ-nigo, R. Casamitjana, F. Nicoletti, R. Gomis, and I. Conget. Insulin lispro is as effective as regular insulin in optimising metabolic control and preserving beta-cell function at onset of type 1 diabetes mellitus. *Diabetes Res.Clin.Pract.* 60 (3):153-159, 2003.	Wrong comparison: short vs. short- acting
BROCK 2011 J Brock, I, B. F. Vind, L. Korsholm, A. Flyvbjerg, J. Frystyk, J. J. Holst, H. Beck-Nielsen, and J. E. Henriksen. Counter-regulatory hormone responses to spontaneous hypoglycaemia during treatment with insulin Aspart or human soluble insulin: a double-blinded randomized cross-over study. *Acta Physiol.* 202 (3):337-347, 2011.	Wrong comparison: short vs. short- acting
BANARER 2008 S. Banarer. Comparison of pharmacokinetics and dynamics of the long-acting	Commentary

Reference	Reason for exclusion
insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. *Diabetes Care* 31 (3):e16, 2008.	
ANON 2011 Anonymous. Insulin degludec/insulin aspart (DegludecPlus) for type 1 diabetes mellitus. Anonymous. Anonymous. National Horizon Scanning Centre (NHSC). 3, 2011. INSULIN_LONG. T1D_RO_Long_071112 DL.	Review Degludec-Aspart
ALBRIGHT 2004 E. S. Albright, R. Desmond, and D. S. Bell. Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. *Diabetes Care* 27 (2):632-633, 2004.	Letter
ANON 2009A Anonymous. Insulin analogues of marginal, if any, benefit. *J.Natl.Med.Assoc.* 101 (8):822-823, 2009.	Abstract: meta-analysis
EINHORN 2012 D. Einhorn, Y. Handelsman, B. W. Bode, L. Endahl, H. Mersebach, and A. B. King. Subjects achieving good glycemic control (Hba1c <7.0%) experience a lower rate of confirmed and nocturnal confirmed hypoglycemia with insulin degludec than with insulin glargine: A meta-analysis of phase 3a trials. *Endocr.Rev.* 33 (3 MeetingAbstracts), 2012.	Conference abstract: meta-analysis
SORLI 2012 C. H. Sorli, M. L. Warren, H. Mersebach, T. Johansen, and D. S. Oyer. Elderly patients experience a lower rate of nocturnal hypoglycemia with insulin degludec than with insulin glargine: A meta-analysis of phase 3a trials. *Endocr.Rev.* 33 (3 MeetingAbstracts), 2012.	Conference abstract: meta-analysis
HOME 2011 P. D. Home, L. Meneghini, J. H. DeVries, J. Jendle, L. Endahl, K. Lyby, T. Johansen, A. P. Roberts, R. E. Ratner, U. Wendisch, and K. I. Birkeland. Insulin degludec in Type 1 diabetes: Comparison of a new-generation ultra-longacting insulin vs. Insulin glargine in a mealtime+basal insulin regimen. *Diabet.Med.* 28:68, 2011.	Conference abstract
HEISE 2011 T. Heise, L. Hermanski, L. Nosek, A. Feldmann, S. Rasmussen, T. K. Stryhn, and H. Haahr. Less pharmacodynamic variability with insulin degludec than insulin glargine. *Diabet.Med.* 28:68, 2011.	Conference abstract: degludec vs. glargine but only 12 days treatment
HIRSCH 2012 I. B. Hirsch, L. F. Meneghini, L. Landstedt-Hallin, S. Rasmussen, N. Lassota, and J. Vora. Less nocturnal hypoglycemia for insulin degludec vs. insulin glargine in subjects with T1DM and baseline A1c of 7.5-8.5%: A meta-analysis. *Diabetes* 61:A299-A300, 2012.	Conference abstract: patient-level meta-analysis of degludec vs. glargine
MENEGHINI 2012A L. F. Meneghini, P.-M. Schumm-Draeger, S. Harris, M.-A. Gall, N. Lassota, and	Conference abstract: meta-analysis

Reference	Reason for exclusion
J. S. Christiansen. Local tolerability of insulin degludec is comparable to insulin glargine: A meta-analysis of t1dm and t2dm. *Diabetes* 61:A230, 2012.	
RUSSELL 2012A D. Russell-Jones, Prato S. Del, M.-A. Gall, N. Lassota, and M. Diamant. Insulin degludec results in consistently lower rates of nocturnal hypoglycemia despite lower FPG levels compared to insulin glargine in seven trials with T1DM or T2DM. *Diabetes* 61:A603, 2012.	Conference abstract: meta-analysis
LI 2011 S. Li, D. Feng, and H. Tian. The efficacy and safety of basal insulin in diabetes mellitus: A systematic review. *Diabetes* 60:A256, 2011.	Conference abstract: systematic review
BUSE 2011 J. B. Buse, S. K. Garg, J. S. Skyler, D. E. Vaughn, and D. B. Muchmore. Comparison of human hyaluronidase + Recombinant Human Insulin (RHI) vs. insulin lispro in a basal-bolus regimen in patients with type 1 diabetes (T1DM). *Diabetes* 60:A18-A19, 2011.	Conference abstract: wrong Treatment – hyaluronidase + human insulin
ZACHARIAH 2011B S. Zachariah, B. Sheldon, F. Shojaee-Moradie, N. Jackson, M. Umpleby, and D. Russell-Jones. Insulin detemir altering food choice as the likely explanation for its weight sparing effects in type 1 diabetes. *Diabetes* 60:A421, 2011.	Conference abstract: have already got enough published RCT evidence for this comparison (detemir vs. NPH)
GARIMELLA 2011 M. Garimella, S. Mitchell, and M. R. Burge. Effects of insulin detemir versus insulin glargine on food intake and satiety factors in type 1 diabetes. *Diabetes* 60:A687, 2011.	Conference abstract: detemir vs. glargine but also fasting and only 24hrs follow-up
PIEBER 2011 T. Pieber, S. Korsatko, G. Kohler, S. Deller, G. Bock, S. Zahiragic, J. Mader, C. Roepstorff, S. Rasmussen, H. Haahr, and S. Heller. Response to induced hypoglycemia in type 1 diabetes: Insulin degludec elicits an enhanced counter-regulatory hormone response compared to insulin glargine. *Diabetes* 60:A138, 2011.	Conference abstract: degludec vs. glargine but only 5 days treatment
VANGOLEN 2011 L. W. Van Golen, M. C. Huisman, R. G. Ijzerman, N. J. Hoetjes, L. A. Schwarte, P. Schober, R. P. Hoogma, M. L. Drent, A. A. Lammertsma, and M. Diamant. Insulin detemir increases cerebral glucose metabolism compared to NPH insulin in human type 1 diabetes: Possible explanation for differences in weight gain? *Diabetes* 60:A421, 2011.	Conference abstract: have already got enough published RCT evidence for this comparison (detemir vs. NPH)
ASSAAD 2010 S. Assaad-Khalil, A. Fayed, and A. A. Aal. Insulin glargine in the early management of diabetic ketoacidosis; A randomized prospective pilot study. *Crit.Care Med.* 38:A70, 2010.	Conference abstract: wrong population – DKA not type 1 diabetes
HERMANSEN 2009A K. Hermansen, S. Heller, M. Andersen, and D. L. Russell-Jones. Insulin detemir reduces hypoglycemic risk at comparable HbAlc values compared to NPH	Conference abstract: have already got enough published RCT evidence for

Reference	Reason for exclusion
Insulin in patients with type 1 diabetes. *Diabetes* 58, 2009.	this comparison (detemir vs. NPH)
HIRSCH 2011 I. B. Hirsch, E. Franek, J.-P. Courreges, H. Mersebach, P. Dykiel, and B. W. Bode. Efficacy and safety of a new basal insulin with a bolus boost (IDegAsp) used once daily in combination with insulin aspart (IAsp) in people with type 1 diabetes. *Diabetes* 60:A292, 2011.	Conference abstract (RCT in type 1 diabetes adults; degludec-aspart vs. detemir; fulfils our inclusion criteria and we need more RCT data on this comparison, so we are contacting authors. – same study as HIRSCH 2011A) Degludec-Aspart
ZACHARIAH 2010 S. Zachariah, B. Sheldon, F. Shojaee-Moradie, N. Jackson, K. Backhouse, S. Johnsen, M. Umpleby, and D. Russell-Jones. Mechanism for the differential effect of the long-acting insulin analog detemir on weight in patients with type 1 diabetes. *Diabetologia* 53:S391, 2010.	Conference abstract: have already got enough published RCT evidence for this comparison (detemir vs. NPH)
VORA 2012 J. Vora, P. Hollander, S. C. Tamer, T. Johansen, and R. Bergenstal. Insulin degludec does not increase antibody formation compared to insulin glargine: An evaluation of phase 3a clinical trials. *Diabetologia* 55:S53-S54, 2012.	Conference abstract: review and wrong outcomes – antibodies to glargine and degludec
VANGOLEN 2012 L. W. Van Golen, D. J. Veltman, R. G. Ijzerman, J. B. Deijen, M. L. Drent, F. Barkhof, and M. Diamant. Insulin detemir reduces activity in reward-related brain regions in response to visual food stimuli in type 1 diabetes: Possible explanation for its weight-sparing effect? *Diabetologia* 55:S281-S282, 2012.	Conference abstract: have already got enough published RCT evidence for this comparison (detemir vs. NPH)
TESTA 2010 M. A. Testa, L. Blonde, J. Gill, R. R. Turner, and D. C. Simonson. Patient-centered outcomes and glycaemic variability in type 1 and type 2 diabetes: A cross-over trial of insulin glargine + glulisine vs premix analogue insulin. *Diabetologia* 53:S395, 2010.	Conference abstract: mixed population of type 1 diabetes and type 2 diabetes and no subgroup analysis.
SKYLER 2012 J. S. Skyler, S. Garg, I. B. Hirsch, T. Blevins, D. E. Vaughn, and D. B. Muchmore. Human hyaluronidase + Rapid Analogue Insulin (RAI) improves postprandial glycaemic control in type 1 diabetes compared to insulin lispro alone. *Diabetologia* 55:S22-S23, 2012.	Conference abstract: wrong treatment – hyaluronidase + human insulin
RUSSELL 2012 D. Russell-Jones, P. Hollander, B. Miranda-Palma, J. G. Cooper, E. Franek, S. Bain, C. B. Djurhuus, S. C. Tamer, and C. Mathieu. Altering the timing of once-daily dosing of insulin degludec achieves similar glycaemic control and safety to dosing at the same time each day in patients with type 1 diabetes. *Diabetologia* 55:S374, 2012.	Conference abstract: wrong comparison – degludec vs. degludec
MENEGHINI 2010 L. Meneghini, P. Home, J. H. DeVries, J. Jendle, L. Endah, K. Lyby, T. Johansen, A. Roberts, R. Ratner, U. Wendisch, and K. I. Birkeland. Insulin deglucec, a	Conference abstract: excluded as full trial has now been published (HOME

Reference	Reason for exclusion
new generation ultra-long acting insulin, in a mealtime + basal regimen in people with type 1 diabetes: Comparison to insulin glargine. *Diabetologia* 53:S388, 2010.	2012) and has been included in this review.
KORSATKO 2012 S. Korsatko, S. Deller, J. Mader, K. Glettler, G. Kohler, G. Bock, M. Urschitz, M. Wolf, H. Hastrup-Nielsen, F. Sondergaard, H. L. Haahr, and T. R. Pieber. Ultra-long pharmacokinetic properties of insulin degludec in younger adults are preserved in geriatric subjects with type 1 diabetes. *Diabetologia* 55:S379-S380, 2012.	Conference abstract
DAGOGO 2000 S. Dagogo-Jack, H. Askari, B. Morrill, L. L. Lehner, B. Kim, and X. Sha. Physiological responses during hypoglycaemia induced by regular human insulin or a novel human analogue, insulin glargine. *Diabetes Obes Metab* 2 (6):373-383, 2000.	Wrong outcomes
HEISE 2004 T. Heise, L. Nosek, B. B. Rã¸Nn, L. Endahl, L. Heinemann, C. Kapitza, and E. Draeger. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes* 53 (6):1614-1620, 2004.	Wrong outcomes: pharmacokinetics and pharmacodynamics.
ARUTCHELVAM 2009 V. Arutchelvam, T. Heise, S. Dellweg, B. Elbroend, I. Minns, and P. D. Home. Plasma glucose and hypoglycaemia following exercise in people with Type 1 diabetes: a comparison of three basal insulins. *Diabet.Med.* 26 (10):1027-1032, 2009.	Wrong outcomes: outcomes measured and compared during and after exercise.
PORCELLATI 2007 F. Porcellati, P. Rossetti, N. R. Busciantella, S. Marzotti, P. Lucidi, S. Luzio, D. R. Owens, G. B. Bolli, and C. G. Fanelli. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. *Diabetes Care* 30 (10):2447-2452, 2007.	Wrong outcomes: pharmacokinetics and pharmacodynamics
WUTTE 2007 A. Wutte, J. Plank, M. Bodenlenz, C. Magnes, W. Regittnig, F. Sinner, B. Rã¸Nn, M. Zdravkovic, and T. R. Pieber. Proportional dose-response relationship and lower within-patient variability of insulin detemir and NPH insulin in subjects with type 1 diabetes mellitus. *Exp.Clin.Endocrinol.Diabetes* 115 (7):461-467, 2007.	Wrong outcomes: pharmacokinetics and pharmacodynamics
RADMAN 2007 M. Radman, D. JurisiÄ‡, D. LjutiÄ‡, R. JerkoviÄ‡, N. KovaciÄ‡, and I. S. Hozo. Assessing glycemia in type 1 diabetic patients using a microdialysis system for continuous glucose monitoring. *Ann.Saudi Med.* 27 (3):166-170, 2007.	Wrong population: age group unclear. Also all patients given education as well as randomised to Glargine vs. NPH
LEPORE 2000 M. Lepore, S. Pampanelli, C. Fanelli, F. Porcellati, L. Bartocci, A. D. Vincenzo, C. Cordoni, E. Costa, P. Brunetti, and G. B. Bolli. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin	Wrong outcomes: pharmacokinetics and pharmacodynamics

Reference	Reason for exclusion
analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49 (12):2142-2148, 2000.	
ASHWELL 2008 S. G. Ashwell, C. Bradley, J. W. Stephens, E. Witthaus, and P. D. Home. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. *Diabetes Care* 31 (6):1112-1117, 2008.	Same study as Ashwell 2006 which was excluded. Glargine vs. NPH but a different meal-time insulin given in each arm, thus not a true comparison of Glargine vs. NPH
VAGUE 2003 P. Vague, J. L. Selam, S. Skeie, I. Leeuw, J. W. Elte, H. Haahr, A. Kristensen, and E. Draeger. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 26 (3):590-596, 2003.	Age group unclear.
KUDVA 2005 Y. C. Kudva, A. Basu, G. D. Jenkins, G. M. Pons, L. L. Quandt, J. A. Gebel, D. A. Vogelsang, S. A. Smith, R. A. Rizza, and W. L. Isley. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. *Diabetes Care* 28 (1):10-14, 2005.	Wrong intervention: Ultralente. Not in BNF; discontinued.
KUDVA 2007 Y. C. Kudva, A. Basu, G. D. Jenkins, G. M. Pons, D. A. Vogelsang, R. A. Rizza, S. A. Smith, and W. L. Isley. Glycemic variation and hypoglycemia in patients with well-controlled type 1 diabetes on a multiple daily insulin injection program with use of glargine and ultralente as basal insulin. *Endocr Pract* 13 (3):244-250, 2007.	Wrong intervention: Ultralente. Not in BNF; discontinued.
HERSHON 2004 K. S. Hershon, T. C. Blevins, C. A. Mayo, and R. Rosskamp. Once-daily insulin glargine compared with twice-daily NPH insulin in patients with type 1 diabetes. *Endocr Pract* 10 (1):10-17, 2004.	Subgroup analysis of an already included study (Ratner 2000)
DAVIS 2007 M. D. Davis, R. W. Beck, P. D. Home, J. Sandow, and F. L. Ferris. Early retinopathy progression in four randomized trials comparing insulin glargine and NPH [corrected] insulin. *Exp.Clin.Endocrinol.Diabetes* 115 (4):240-243, 2007.	Meta-analysis of 5 RCTs. We already have included the relevant RCTs (3 included, 2 did not meet our inclusion criteria as were type 2 diabetes).
MULLINS 2007 P. Mullins, P. Sharplin, H. Yki-Jarvinen, M. C. Riddle, and H. U. Haring. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin.Ther.* 29 (8):1607-1619, 2007.	IPD of Glargine vs. NPH. Hpwever som of the studies included did not meet our inclusion criteria – some were TD and one of the type 1 diabetes we excluded (Ashwell 2006) because the meal-time insulin used was different in each arm.
HERWIG 2007 J. Herwig, G. Scholl-Schilling, and H. Böhles. Glycaemic control and	Extension study of a paediatric study and not

Reference	Reason for exclusion
hypoglycaemia in children, adolescents and young adults with unstable type 1 diabetes mellitus treated with insulin glargine or intermediate-acting insulin. *J.Pediatr.Endocrinol.Metab.* 20 (4):517-525, 2007.	stated to be randomised in this extension part.
KUDVA 2005 Y. C. Kudva, A. Basu, G. D. Jenkins, G. M. Pons, L. L. Quandt, J. A. Gebel, D. A. Vogelsang, S. A. Smith, R. A. Rizza, and W. L. Isley. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. *Diabetes Care* 28 (1):10-14, 2005.	Wrong comparison: Ultralente (not licenced in UK/not in BNF)
KUDVA 2007 Y. C. Kudva, A. Basu, G. D. Jenkins, G. M. Pons, D. A. Vogelsang, R. A. Rizza, S. A. Smith, and W. L. Isley. Glycemic variation and hypoglycemia in patients with well-controlled type 1 diabetes on a multiple daily insulin injection program with use of glargine and ultralente as basal insulin. *Endocr Pract* 13 (3):244-250, 2007.	Wrong comparison: Ultralente (not licenced in UK/ not in BNF)
ROSAK 2008 C. Rosak, R. Jung, and U. Hofmann. Insulin glargine maintains equivalent glycemic control and better lipometabolic control than NPH insulin in type 1 diabetes patients who missed a meal. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et mÃ©tabolisme* 40 (8):544-548, 2008.	Wrong follow-up time: 1 week (but meets all other inclusion criteria)
DANNE 2003 T. Danne, K. LÃ¼pke, K. Walte, W. Schuetz, and M. A. Gall. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. *Diabetes Care* 26 (11):3087-3092, 2003.	Wrong follow-up time: single dose given (but meets all other inclusion criteria)
HEISE 2012 T. Heise, L. Hermanski, L. Nosek, A. Feldman, S. Rasmussen, and H. Haahr. Insulin degludec: Four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabestes Obes.Metab.* 14 (9):859-864, 2012.	Wrong follow-up time: 12 days (but meets all other inclusion criteria)
SANCHES 2011 A. C. Sanches, C. J. Correr, R. Venson, and R. Pontarolo. Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons. *Diabetes Res.Clin.Pract.* 94 (3):333-339, 2011.	NMA – used for references but only searched until 2000.
TSUJINO 2012 D. Tsujino, R. Nishimura, A. Morimoto, N. Tajima, and K. Utsunomiya. A crossover comparison of glycemic variations in japanese patients with type 1 diabetes receiving insulin glargine versus insulin detemir twice daily using continuous glucose monitoring (CGM): J COLLECTION (Jikei COmparison of Lantus and LEvemir with Cgm for Thinking Insulin OptimizatioN). *Diabetes Technol.Ther.* 14 (7):596-601, 2012.	Wrong outcomes reported: only blood glucose and time in hypoglycaemia (not our pre-specified outcomes).
YAMADA 2014 K. Yamada, H. Nakayama, S. Sato, Y. Tajiri, H. Kaku, I. Tokubuchi, T. Kato, E. Soejima, and T. Ohki. A randomized crossover study of the efficacy and safety	Glargine vs. degludec Unclear which SA insulin used; only 2 wks follow-

Reference	Reason for exclusion
of switching from insulin glargine to insulin degludec among patients with type 1 diabetes. *Diabetol.Int.* 5 (1):74-77, 2014.	up/treatment duration. Otherwise meets inclusion criteria.
MENEGHINI 2013 L. Meneghini, S. L. Atkin, S. C. Gough, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care* 36 (4):858-864, 2013.	Type 2 diabetes
PEREZ 2013 M. Perez-Maraver, J. Caballero-Corchuelo, A. Boltana, R. Insa, J. Soler, and E. Montanya. Comparison of human insulin and insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index). *Acta Diabetol.* 50 (4):529-535, 2013.	Different SA insulin used in each arm, thus not true comparison of Glargine vs. NPH.
HERRING 2013 R. Herring, F. Shojaee-Moradie, N. Jackson, R. Jones, M. Umpleby, and D. L. Russell-Jones. The effects of subcutaneous insulin NPH and detemir on glucose flux and lipolysis following a period of insulin withdrawal in patients with type 1 diabetes. *Diabetes* 62:A492, 2013.	Conference abstract. Got enough fully published data on this comparison already.
SANCHES 2011 A. C. Sanches, C. J. Correr, R. Venson, and R. Pontarolo. Revisiting the efficacy of long-acting insulin analogues on adults with type 1 diabetes using mixed-treatment comparisons. *Diabetes Res.Clin.Pract.* 94 (3):333-339, 2011.	Already ordered and excluded pre-reruns.
HIRSCH 2014 I. B. Hirsch, S. N. DuBose, K. M. Miller, D. M. Maahs, and R. W. Beck. Twice daily versus once daily basal insulin does not result in better glycemic outcomes among MDI patients with T1D. *Diabetes Technol.Ther.* 16:A91, 2014.	Conference abstract (have enough fully published data on this already); for LA insulin once vs. twice question.
AGESEN 2013 R. M. Agesen, P. L. Kristensen, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, P. Hougaard, H.-H. Parving, B. Thorsteinsson, L. Tarnow, and U. Pedersen-Bjergaard. Effect of insulin analogues on frequency of mild hypoglycaemia in patients with type 1 diabetes and recurrent severe hypoglycaemia: The prospective, controlled HypoAna trial. *Diabetologia* 56:S239, 2013.	Conference abstract
BAY 2013A C. Bay, Kristensen P. Lommer, U. Pedersen-Bjergaard, L. Tarnow, and B. Thorsteinsson. Nocturnal hypoglycaemia: Effect of insulin analogues compared to human insulin in type 1 diabetic patients prone to severe hypoglycaemia. *Diabetologia* 56:S239, 2013.	Conference abstract
BECKER 2014 R. H. A. Becker, I. Nowotny, L. Teichert, K. Bergmann, and C. Kapitza. Low within-and between-day variability in exposure to new insulin glargine 300	Conference abstract

Reference	Reason for exclusion
U.ML-1. *Diabetes* 63:A228, 2014.	
BLEVINS 2014 T. Blevins, D. Dahl, J. Rosenstock, L. Ilag, W. J. Huster, R. K. Pollom, and M. J. Prince. Similar efficacy and safety with LY2963016 insulin glargine compared with lantus insulin glargine in patients with T1DM: The element 1 study. *Diabetes* 63:A19, 2014.	Conference abstract
BODE 2013B B. W. Bode, T. Heise, T. R. Pieber, T. Johansen, S. Rasmussen, and D. L. Russell-Jones. Higher rates of confirmed hypoglycaemia are associated with greater within-subject variability in fasting blood glucose in type 1 and type 2 diabetes: A meta-analysis. *Diabetologia* 56:S423, 2013.	Conference abstract
DEEG 2014 M. Deeg, L. Ilag, W. J. Huster, R. K. Pollom, J. Zielonka, M. J. Prince, and R. J. Konrad. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus insulin glargine in patients with T1DM or T2DM. *Diabetes* 63:A19, 2014.	Conference abstract
FRIER 2013 B. M. Frier, D. Russell-Jones, and T. Heise. A comparison of insulin detemir and neutral protamine Hagedorn (isophane) insulin in the treatment of diabetes: a systematic review. *Diabestes Obes.Metab.* 15 (11):978-986, 2013.	SR – used as source of refernces.
FRYSTYK 2014 J. Frystyk, Z. Ma, T. Laursen, T. Lauritzen, and J. S. Christiansen. Short-term effects of NPH insulin, insulin detemir, and insulin glargine on the IGF-IGFBP-GH axis in patients with type 1 diabetes. *Diabetes* 63:A489-A490, 2014.	Conference abstract
GODMAN 2014 B. Godman, Souza A. De, F. Acurcio, and Jr Guerra. Insulin glargine in a Brazilian state: An assessment of drug utilization, effectiveness and value to provide future direction. *Basic Clin.Pharmacol.Toxicol.* 115:72, 2014.	Conference abstract
GOLDMAN 2013 JD. Goldman-Levine, DK. Patel, and DM. Schnee. Insulin degludec: a novel basal insulin analogue. *Ann.Pharmacother.* 47 (2):269-277, 2013.	SR – used as source of refernces.
HEISE 2012 T. Heise, L. Hermanski, L. Nosek, A. Feldman, S. Rasmussen, and H. Haahr. Insulin degludec: Four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. *Diabetes Obesity and Metabolism* 14 (9):859-864, 2012.	Already found study in pre-rerun literature search. Excluded from review as only 12 days follow-up time.
HEISE 2014 T. Heise, X. Zhang, E. C. Q. Lam, M. E. Seger, D. Coutant, L. Chua, and H. Linnebjerg. Duration of action of 2 insulin glargine products, LY2963016 and Lantus, in subjects with type I diabetes mellitus (T1DM). *Diabetes* 63:A228, 2014.	Conference abstract

Reference	Reason for exclusion
HELLER 2012 S. Heller, J. Buse, M. Fisher, S. Garg, M. Marre, L. Merker, E. Renard, D. Russell-Jones, A. Philotheou, A. M. Francisco, H. Pei, and B. Bode. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. *Lancet* 379 (9825):1489-1497, 2012.	Already found in pre-rerun literature search. Was included as part of the review.
HELLER 2013B S Heller, B Bode, Plamen Kozlovski, and Anne Louise Svendsen. Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. *J Diabetes* 5 (4):482-491, 2013.	SR/MA – used as source of refernces.
HELLER 2014 S. R. Heller, C. Mathieu, R. Kapur, M. L. Wolden, and B. Zinman. Rate ratios for nocturnal confirmed hypoglycemia with insulin degludec vs. Insulin glargine using different definitions. *Diabetes* 63:A106, 2014.	Conference abstract
HELLER 2014A S. Heller, S. C. L. Gough, D. S. Oyer, K. H. Jensen, O. Kinduryte, and A. Philis-Tsimikas. Insulin degludec and insulin glargine have similar incidence of exercise-related hypoglycaemia. *Diabet Med* 31:62, 2014.	Conference abstract
HERRING 2013 R. Herring, F. Shojaee-Moradie, N. Jackson, R. Jones, M. Umpleby, and D. L. Russell-Jones. The effects of subcutaneous insulin NPH and detemir on glucose flux and lipolysis following a period of insulin withdrawal in patients with type 1 diabetes. *Diabetes* 62:A492, 2013.	Conference abstract
HERRING 2014 R. Herring, F. Shojaee-Moradie, M. Umpleby, N. Jackson, R. Jones, D. Derk-Jan, R. Knight, and D. Russell-Jones. Subcutaneous insulin detemir compared with NPH insulin increases brain potential responses with similar systemic metabolic effects in people with Type 1 diabetes. *Diabet Med* 31:62, 2014.	Conference abstract
HOD 2014 M Hod, ER. Mathiesen, L Jovanovic, DR. McCance, M Ivanisevic, S Duran-Garcia, L Brondsted, A Nazeri, and P Damm. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J Matern Fetal Neonatal Med* 27 (1):7-13, 2014.	Wrong population: pregnant women.
HOME 2012 P. D. Home, L. Meneghini, U. Wendisch, R. E. Ratner, T. Johansen, T. E. Christensen, J. Jendle, A. P. Roberts, and K. I. Birkeland. Improved health status with insulin degludec compared with insulin glargine in people with Type1 diabetes. *Diabet Med* 29 (6):716-720, 2012.	Already found in pre-rerun literature search. Was included as part of the review.
HOPKINSON 2014 H. E. Hopkinson, R. M. Jacques, K. J. Gardner, S. A. Amiel, and P. M. Mansell. A twice daily basal insulin (BI) replacement regimen achieves better	Conference abstract

Reference	Reason for exclusion
glycaemic control than a once daily regimen during structured education in adults with Type 1 diabetes in routine UK clinical practice. *Diabet Med* 31:7, 2014.	
KERLAN 2013 V Kerlan, D Gouet, M Marre, and E Renard. Use of insulin degludec, a new basal insulin with an ultra-long duration of action, in basal-bolus therapy in type 1 and type 2 diabetes. *Ann Endocrinol (Paris)* 74 (5-6):487-490, 2013.	Overview of a previously published trial, which we have already included in our review (HELLER 2012).
KOEHLER 2014 G. Koehler, G. Treiber, A. Wutte, S. Korsatko, J. K. Mader, B. Semlitsch, and T. R. Pieber. Pharmacodynamics of the long-acting insulin analogues detemir and glargine following single-doses and under steady-state conditions in patients with type 1 diabetes. *Diabestes Obes.Metab.* 16 (1):57-62, 2014.	Wrong follow-up time: 30 hours
KOEHLER 2014A G Koehler, S Heller, S Korsatko, C Roepstorff, Soren Rasmussen, Hanne Haahr, and Thomas R. Pieber. Insulin degludec is not associated with a delayed or diminished response to hypoglycaemia compared with insulin glargine in type 1 diabetes: a double-blind randomised crossover study. *Diabetologia* 57 (1):40-49, 2014.	Wrong follow-up time: 5 days
KORSATKO 2013A S. Korsatko, K. Glettler, K. J. Olsen, A. Wutte, G. Bock, G. Koehler, J. K. Mader, B. Semlitsch, and T. R. Pieber. A direct comparison of the pharmacodynamic properties of insulin detemir and neutral protamine lispro insulin in patients with type 1 diabetes. *Diabestes Obes.Metab.* 15 (3):241-245, 2013.	Wrong follow-up time: 32 hours
KORSATKO 2014 S. Korsatko, S. Deller, J. K. Mader, K. Glettler, G. Koehler, G. Treiber, M. Urschitz, M. Wolf, H. Hastrup, F. Sondergaard, H. Haahr, and T. R. Pieber. Ultra-long pharmacokinetic properties of insulin degludec are comparable in elderly subjects and younger adults with type 1 diabetes mellitus. *Drugs Aging* 31 (1):47-53, 2014.	Wrong follow-up time: 6 days
MONAMI 2013 M Monami and Edoardo Mannucci. Efficacy and safety of degludec insulin: a meta-analysis of randomised trials. *Curr.Med.Res.Opin.* 29 (4):339-342, 2013.	SR/MA – used as a source of references.
MONAMI 2013B M. Monami, L. Filippi, A. Ungar, F. Sgrilli, A. Antenore, I. Dicembrini, P. Bagnoli, N. Marchionni, C. M. Rotella, and E. Mannucci. Further data on beta-blockers and cancer risk: observational study and meta-analysis of randomized clinical trials. *Curr.Med.Res.Opin.* 29 (4):369-378, 2013.	Wrong intervention.
MORROW 2013 L. A. Morrow, M. Hompesch, S. J. Jacober, S. L. Choi, Y. Qu, and V. Sinha. LY2605541 exhibits a flatter glucodynamic profile than insulin glargine at steady state in subjects with type 1 diabetes. *Diabetologia* 56:S414, 2013.	Conference abstract
OYER 2013	Conference abstract

Reference	Reason for exclusion
D. S. Oyer, S. Heller, S. C. L. Gough, K. H. Jensen, O. Kinduryte, and A. Philis-Tsimikas. Exercise-related hypoglycaemia occurs at similar frequency with insulin degludec and insulin glargine. *Diabetologia* 56:S84-S85, 2013.	
PEDERSEN 2013 U. Pedersen-Bjergaard, P. L. Kristensen, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, P. Hougaard, H.-H. Parving, B. Thorsteinsson, and L. Tarnow. The effect on insulin analogues on the risk of severe hypoglycaemia in patients with type 1 diabetes and recurrent severe hypoglycaemia: The HypoAna trial. *Diabetologia* 56:S84, 2013.	Conference abstract
PEDERSEN 2014A U Pedersen-Bjergaard, PL Kristensen, H Beck-Nielsen, K Norgaard, H Perrild, JS Christiansen, T Jensen, P Hougaard, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. *Lancet Diabetes Endocrinol* 2 (7):553-561, 2014.	Wrong intervention and comparison: patienmts given different SA insulins in each of the arms. Should be the same SA insulin and only the LA insulin different.
POLONSKY 2014 W. Polonsky, L. Traylor, L. Gao, W. Wei, B. Ameer, A. Stuhr, and A. Vlajnic. Improved treatment satisfaction in T1DM patients treated with insulin glargine (GLA) vs. NPH insulin. *Diabetes* 63:A200-A201, 2014.	Conference abstract
RATNER 2013 R. E. Ratner, S. C. L. Gough, C. Mathieu, S. Del Prato, B. Bode, H. Mersebach, L. Endahl, and B. Zinman. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabestes Obes.Metab.* 15 (2):175-184, 2013.	Data from trials already included in the review. Plus not enough details given to use data from this publication.
SORLI 2013 C Sorli, M Warren, D Oyer, H Mersebach, T Johansen, and SCL. Gough. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: a meta-analysis of phase IIIa trials. *Drugs Aging* 30 (12):1009-1018, 2013.	SR/MA – used as a source of references.
VANGOLEN 2013 LW. van Golen, RG. IJzerman, MC. Huisman, JF. Hensbergen, RP. Hoogma, ML. Drent, AA. Lammertsma, and M Diamant. Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after treatment with insulin detemir and NPH insulin: a randomized controlled crossover trial. *Diabetes Care* 36 (12):4050-4056, 2013.	Already have this study and included in review (GOLEN 2013)
VANGOLEN 2014 LW. van Golen, DJ. Veltman, RG. IJzerman, JB Deijen, AC. Heijboer, F Barkhof, ML. Drent, and M Diamant. Effects of insulin detemir and NPH insulin on body weight and appetite-regulating brain regions in human type 1 diabetes: a randomized controlled trial. *PloS One* 9 (4):e94483, 2014.	Data of this study has previously been published, and has been included in review (GOLEN 2013)
WALLACE 2014 JP. Wallace, JL. Wallace, and MS McFarland. Comparing dosing of Basal	SR – used as source of references.

Reference	Reason for exclusion
insulin analogues detemir and glargine: is it really unit-per-unit and dose-per-dose? *Ann.Pharmacother.* 48 (3):361-368, 2014.	
Additional studies from old GL, TA and cross-referencing SRs, MAs and other GLs	
WARREN 2004 E. Warren, E. Weatherley-Jones, J. Chilcott, and C. Beverley. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. *Health Technol.Assess.* 8 (45):iii-41, 2004.	HTA report – basis of the NICE TA on glargine. Used for references.
PAMPANELLI 1996 S. Pampanelli, C. Fanelli, C. Lalli, M. Ciofetta, P. Sindaco, M. Lepore, F. Modarelli, A. M. Rambotti, L. Epifano, A. Vincenzo, L. Bartocci, B. Annibale, P. Brunetti, and G. B. Bolli. Long-term intensive insulin therapy in IDDM: effects on HbA1c, risk for severe and mild hypoglycaemia, status of counterregulation and awareness of hypoglycaemia. *Diabetologia* 39 (6):677-686, 1996.	Wrong comparison: no drug comparison group.
TUNBRIDGE 1989 (ID 248) F. K. E. Tunbridge, A. Newens, P. D. Home, S. N. Davis, M. Murphy, J. M. Burrin, K. G. M. M. Alberti, and I. Jensen. Double-blind crossover trial of isophane (NPH)- and lente-based insulin regimens. *Diabetes Care* 12 (2):115-119, 1989.	Wrong comparison: NPH vs. Ultralente – ultralente has been discontinued.
HAAKENS 1989 (ID 1057) K. Haakens, K. F. Hanssen, K. Dahl-Jorgensen, S. Vaaler, P. Torjesen, and K. Try. Early morning glycaemia and the metabolic consequences of delaying breakfast/morning insulin. A comparison of continuous subcutaneous insulin infusion and multiple injection therapy with human isophane or human ultralente insulin at bedtime in insulin-dependent diabetics. *Scandinavian Journal of Clinical & Laboratory Investigation* 49 (7):653-659, 1989.	Wrong comparison: NPH vs. Ultralente – ultralente has been discontinued.

K.4.3 Mixed insulin

Reference	Reason for exclusion
CHEN 2005 J. W. Chen, T. Lauritzen, J. J. Christiansen, L. H. Jensen, W. H. Clausen, and J. S. Christiansen. Pharmacokinetic profiles of biphasic insulin aspart 30/70 and 70/30 in patients with Type 1 diabetes: a randomized double-blinded crossover study. *Diabet.Med.* 22 (3):273-277, 2005.	BiApsart 70/30 is not available in the UK.
GRONDA 1991 D. Gronda, L. Cacciabue, C. Mezzogori, M. Rossin, and E. Ronchi. [Absorption of short-acting insulin mixed with different slow-release formulations]. *La Clinica terapeutica* 136 (2):95-100, 1991.	Not in English.
GAO 2009 Y. Gao, C. Y. Pan, D. J. Zou, Z. R. Xu, X. M. Liu, and X. H. Guo. [Postprandial glycemic control using insulin aspart with NPH in inadequately controlled diabetics]. *Zhonghua yi xue za zhi* 89 (28):1960-1963, 2009.	Not in English.

Reference	Reason for exclusion
RENNER 2003	Not in English.
CENGIZ 2009 E. Cengiz, W. V. Tamborlane, M. Martin, and S. A. Weinzimer. Should we mix lispro with glargine? Removing the guesswork by euglycemic clamp studies. *Diabetes* 58, 2009	Abstract. Wrong population: mainly young people <18 years old.
CENGIZ 2010 E Cengiz, WV. Tamborlane, M Martin-Fredericksen, J Dziura, and S A. Weinzimer. Early pharmacokinetic and pharmacodynamic effects of mixing lispro with glargine insulin: results of glucose clamp studies in youth with type 1 diabetes. *Diabetes Care* 33 (5):1009-1012, 2010.	Abstract. Wrong population: mainly young people <18 years old.
HASSAN 2008 K. Hassan, L. M. Rodriguez, S. E. Johnson, S. Tadlock, and R. A. Heptulla. A randomized, controlled trial comparing twice-a-day insulin glargine mixed with rapid-acting insulin analogs versus standard neutral protamine Hagedorn (NPH) therapy in newly diagnosed type 1 diabetes. *Pediatrics* 121 (3):e466-e472, 2008	Wrong population: children
THORISDOTTIR 2009 R. L. Thorisdottir, T. Parkner, J. W. Chen, N. Ejskjaer, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of biphasic insulin aspart 30, 50, 70 and pure insulin aspart: a randomized, quadruple crossover study. *Basic Clin.Pharmacol.Toxicol.* 104 (3):216-221, 2009.	Wrong follow-up: only 800 minutes.
CHEN 2005A J. W. Chen, J. Frystyk, T. Lauritzen, and J. S. Christiansen. Impact of insulin antibodies on insulin aspart pharmacokinetics and pharmacodynamics after 12-week treatment with multiple daily injections of biphasic insulin aspart 30 in patients with type 1 diabetes. *EUR.J.ENDOCRINOL.* 153 (6):907-913, 2005.	Subgroup analysis of an RCT but only looks at one arm of the trial.
ARAI 2010 K. Arai, K. Hirao, M. Yamauchi, H. Takagi, M. Kobayashi, and Japan Diabetes Clinical Data Management Study Group. Influence of BMI, age and duration of diabetes mellitus on glycaemic control with twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart (JDDM 18): retrospective reanalysis of a 6-month, randomized, open-label, multicentre trial in Japan. *Clin.Drug.Invest.* 30 (1):35-40, 2010.	Wrong population: type 2 diabetes
GARBER 2006 AJ. Garber. Premixed insulin analogues for the treatment of diabetes mellitus. *Drugs* 66 (1):31-49, 2006	Wrong population: type 2 diabetes
VELUSSI 1989 M. Velussi, A. Cernigoi, C. Puglisi, G. Bernardi, P. Miniussi, L. Viezzoli, F. Dapas, and E. Duner. Experimental study of the different potencies of biosynthetic and semisynthetic human insulin mixtures in the treatment of insulin-dependent diabetics. *Curr.Ther.Res.Clin.Exp.* 46 (2):390-398, 1989.	Not an RCT – pts matched in each group. Age 15-40 years but does not give % who were >18 years old.
DAVIES 1988	Wrong follow-up: only

Reference	Reason for exclusion
R. R. Davies, J. McEwen, T. A. Moreland, C. Durnin, and R. W. Newton. Improvement in morning hyperglycaemia with basal human ultratard and prandial human actrapid insulin--a comparison of multiple injection regimens. *Diabet.Med.* 5 (7):671-675, 1988.	24hrs.
LUNETTA 1987 M. Lunetta, Mauro M. Di, and Bella G. La. Miscibility of biosynthetic intermediate-acting protamine insulin with short-acting insulin. *MED.SCI.RES.* 15 (3):155-156, 1987.	Wrong follow-up: only 240 mins.
ANDERSON 1997A J. H. Anderson, Jr., R. L. Brunelle, P. Keohane, V. A. Koivisto, M. E. Trautmann, L. Vignati, and R. DiMarchi. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Arch.Intern.Med.* 157 (11):1249-1255, 1997.	Wrong population: type 2 diabetes
BURGE 1997 M. R. Burge, D. L. Waters, J. H. Holcombe, and D. S. Schade. Prolonged efficacy of short acting insulin lispro in combination with human ultralente in insulin-dependent diabetes mellitus. *J.Clin.Endocrinol.Metab.* 82 (3):920-924, 1997.	Wrong follow-up: only 24hrs.
CLEMENTS 2008 M. R. Clements, J. Tits, B. T. Kinsley, J. Rastam, H. H. Friberg, and R. J. Ligthelm. Improved glycaemic control of thrice-daily biphasic insulin aspart compared with twice-daily biphasic human insulin; a randomized, open-label trial in patients with type 1 or type 2 diabetes. *Diabestes Obes.Metab.* 10 (3):229-237, 2008.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis, and only 14% are type 1 diabetes.
KEATING 2012 Gillian M. Keating. Insulin detemir: a review of its use in the management of diabetes mellitus. *Drugs* 72 (17):2255-2287, 2012.	SR – used as a source of references. Does not look at mixed insulins.
GOICOLEA 1987 I. Goicolea, A. Quiroga, and J. A. Vazquez. The effect of insulin mixtures in type I diabetics: influence of the intermediate acting insulin on the action of short acting insulin. *Diabete Metab* 13 (4):467-470, 1987.	Wrong follow-up: only 240 mins.
MALONE 2000 J. K. Malone, H. Yang, J. R. Woodworth, J. Huang, B. N. Campaigne, J. P. Halle, J. F. Yale, and L. D. Grossman. Humalog Mix25 offers better mealtime glycemic control in patients with type 1 or type 2 diabetes. *Diabetes Metab.* 26 (6):481-487, 2000.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis for our outcomes of interest, and only 53% are type 1 diabetes.
MA 2012 Z. Ma, T. Parkner, J. S. Christiansen, and T. Laursen. IDegAsp: A novel soluble insulin analogs combination. *Expert Opin.Biol.Ther.* 12 (11):1533-1540, 2012.	SR – used as a source of references.
CERIELLO 2012	Wrong intervention. Lispro

Reference	Reason for exclusion
A Ceriello, F Cremasco, E Romoli, A Rossi, and R Gentilella. Insulin lispro protamine suspension in the treatment of patients with type 1 and type 2 diabetes mellitus: a systematic review of published data. *Expert Opin.Pharmacother.* 13 (2):255-281, 2012.	given as a basal insulin. Does not look at mixed insulins.
WEINGES 1982 K. Weinges, M. Ehrhardt, G. Nell, and F. Enzmann. Pharmacodynamics of human insulin (recombinant DNA) - regular, NPH, and mixtures - obtained by the Gerritzen method in healthy volunteers. *Diabetes Care* 5 (Suppl. 2):67-70, 1982.	Healthy population.
DAVIDSON 2005 J. Davidson, P. Vexiau, D. Cucinotta, J. Vaz, and R. Kawamori. Biphasic insulin aspart 30: Literature review of adverse events associated with treatment. *Clin.Ther.* 27 (SUPPL. 2):S75-S88, 2005.	SR – used as a source of references.
HERMANSEN 2002 K Hermansen, S Vaaler, S Madsbad, M Dalgaard, M Zander, K Begtrup, and K Soendergaard. Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. *Metabolism.* 51 (7):896-900, 2002.	Wrong follow-up: only 1 day.
SIMPSON 2007 D. Simpson, P. L. McCormack, G. M. Keating, and K. A. Lyseng-Williamson. Insulin lispro: A review of its use in the management of diabetes mellitus. *Drugs* 67 (3):407-434, 2007.	SR – used as a source of references.
RAJAKHAN 2007 Nazia Raja-Khan, Sarah S. Warehime, and Robert A. Gabbay. Review of biphasic insulin aspart in the treatment of type 1 and 2 diabetes. *Vasc Health Risk Manag* 3 (6):919-935, 2007.	SR – used as a source of references.
VALENSI 2009 P Valensi. Biphasic insulin aspart 30/70 (BIAsp 30) in the treatment of type 1 and type 2 diabetes. *Diabetes Metab Syndr Obes* 2:61-71, 2009.	SR – used as a source of references.
BOEHM 2002A B. O. Boehm, P. D. Home, C. Behrend, N. M. Kamp, and A. Lindholm. Erratum: Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and type 2 diabetic patients (Diabetic Medicine (2002) 19 (393-399)). *Diabet.Med.* 19 (9):797, 2002.	Erratum only.
DRANITSARIS 2000 G. Dranitsaris, C. J. Longo, and L. D. Grossman. The economic value of a new insulin preparation, Humalog Mix 25. Measured by a willingness-to-pay approach. *Pharmacoeconomics* 18 (3):275-287, 2000.	Data from the Roach 1999 RCT. Health economics paper.
ANON 2011A	Report about studies of DegAsp – not an RCT.
AHMED 1998A A. B. Ahmed, J. Mallias, and P. D. Home. Optimization of evening insulin dose	Wrong follow-up: only 1 day.

Reference	Reason for exclusion
in patients using the short-acting insulin analog lispro. *Diabetes Care* 21 (7):1162-1166, 1998.	
RASSAM 1999 A. G. Rassam, T. M. Zeise, M. R. Burge, and D. S. Schade. Optimal administration of lispro insulin in hyperglycemic type 1 diabetes. *Diabetes Care* 22 (1):133-136, 1999.	Wrong follow-up: only 1 day.
KAPLAN 2004 Walid Kaplan, Luisa M. Rodriguez, O'Brian E. Smith, Morey W. Haymond, and Rubina A. Heptulla. Effects of mixing glargine and short-acting insulin analogs on glucose control. *Diabetes Care* 27 (11):2739-2740, 2004.	Wrong follow-up: only 10 days; wrong outcomes: blood glucose only.
LINDHOLM 2002 A Lindholm, LB. Jensen, P D. Home, P Raskin, B O. Boehm, and J Rastam. Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. *Diabetes Care* 25 (5):876-882, 2002.	Report of 4 x RCTs but wrong outcomes – Insulin antibodies only.
RAVE 1999 K. Rave, L. Heinemann, L. Puhl, U. Gudat, J. R. Woodworth, C. Weyer, and T. Heise. Premixed formulations of insulin lispro. Activity profiles in type 1 diabetic patients. *Diabetes Care* 22 (5):865-866, 1999.	Abstract/short report. Wrong follow-up: only 19 hours.
LANDGRAF 1982 R. Landgraf, S. Kammerer, and T. Bock. Crossover study with human insulin (recombinant DNA) in type I diabetic subjects. *Diabetes Care* 5 (Suppl 2):39-42, 1982.	Wrong follow-up: only 1 week.
LI 2009A Y Li, Qiang Li, C jiang Li, C jiang Wang, Y man Zheng, M Issa, and J Zhang. Comparison of HbA1c in Chinese patients with type 1 or type 2 diabetes randomized to twice daily insulin lispro low mix 25 or twice daily human insulin mix 30/70. *Chin.Med.J.(Engl).* 122 (21):2540-2546, 2009.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis, and only 3% are type 1 diabetes.
SAILER 1982 D. Sailer, T. Ludwig, and S. Kolb. Comparison of the activity profiles of two fixed combinations of regular/NPH human insulin (recombinant DNA) of different compositions with a fixed regular/NPH porcine insulin combination (PPI) in insulin-dependent diabetic individuals. *Diabetes Care* 5 Suppl 2:57-59, 1982.	Wrong follow-up: only 4 days.
RENNER 1982 R. Renner, K. Vocke, and K. D. Hepp. Search for the most practical regular/NPH mixtures for type I diabetic patients. *Diabetes Care* 5 Suppl 2:53-56, 1982.	Wrong follow-up: only 24 hours.
TESTA 2010 M. A. Testa, L. Blonde, J. Gill, R. R. Turner, and D. C. Simonson. Patient-centered outcomes and glycaemic variability in type 1 and type 2 diabetes: A cross-over trial of insulin glargine + glulisine vs premix analogue insulin. *Diabetologia* 53:S395, 2010.	Conference abstract. Have got the fully published paper (TESTA 2012)

Reference	Reason for exclusion
ROLAND 1984 J. M. Roland. Need stable diabetics mix their insulins? *Diabet.Med.* 1 (1):51-53, 1984.	Wrong follow-up: only 4 days.
MA 2012A Z. Ma, T. Parkner, J. Frystyk, T. Laursen, T. Lauritzen, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: A randomized, quadruple crossover study. *Diabetes Technol.Ther.* 14 (7):589-595, 2012.	Wrong follow-up: only 720 hours.
HEISE 2008 T. Heise, U. Eckers, K. Kanc, J. N. Nielsen, and L. Nosek. The pharmacokinetic and pharmacodynamic properties of different formulations of biphasic insulin aspart: a randomized, glucose clamp, crossover study. *Diabetes Technol.Ther.* 10 (6):479-485, 2008.	Wrong follow-up: only 28 hours.
ROACH 2003 P. Roach, J. Woodworth, U. Gudat, B. Cerimele, F. Diebler, M. Pein, and M. Dreyer. A 75% insulin lispro/25% NPL mixture provides a longer duration of insulin activity compared with insulin lispro alone in patients with Type 1 diabetes. *Diabet.Med.* 20 (11):946-952, 2003.	Wrong follow-up: only 72 hours.
CENGIZ 2012 E. Cengiz, K. L. Swan, W. V. Tamborlane, J. L. Sherr, M. Martin, and S. A. Weinzimer. The alteration of aspart insulin pharmacodynamics when mixed with detemir insulin. *Diabetes Care* 35 (4):690-692, 2012.	Wrong follow-up: only 300 mins.
LALLI 1999 (1066) C. Lalli, M. Ciofetta, P. Del Sindaco, E. Torlone, S. Pampanelli, P. Compagnucci, M. G. Cartechini, L. Bartocci, P. Brunetti, and G. B. Bolli. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 22 (3):468-477, 1999.	Wrong intervention: not mixed insulin.
HIRSCH 2011 I. B. Hirsch, E. Franek, J.-P. Courreges, H. Mersebach, P. Dykiel, and B. W. Bode. Efficacy and safety of a new basal insulin with a bolus boost (IDegAsp) used once daily in combination with insulin aspart (IAsp) in people with type 1 diabetes. *Diabetes* 60:A292, 2011.	**Degludec-Aspart mix.** Conference abstract. Now published as full RCT and included in this review (HIRSCH 2012B).
HIRSCH 2011A I. Hirsch, E. Franek, J. P. Courreges, H. Mersebach, P. Dykiel, and B. W. Bode. IDegAsp, a soluble insulin combination of ultra-long-acting insulin degludec and insulin aspart, used once daily in basal-bolus treatment with insulin aspart in type 1 diabetes. *Diabetologia* 54:S427, 2011.	**Degludec-Aspart mix.** Conference abstract. Now published as full RCT and included in this review (HIRSCH 2012B).
CORCORAN 1985 J. S. Corcoran and J. S. Yudkin. How inaccurate is insulin mixing? Patient variability and syringe dead space effect. *Diabetic medicine: a journal of the*	Wrong outcomes – accuracy and reproducibility of insulin mixing.

Reference	Reason for exclusion
British Diabetic Association 2 (2):131-133, 1985.	
BOTT 2005 S. Bott, C. Tusek, L. Heinemann, H. H. Friberg, and T. Heise. The pharmacokinetic and pharmacodynamic properties of biphasic insulin aspart 70 (BIAsp 70) are significantly different from those of biphasic insulin aspart 30 (BIAsp 30). *Exp.Clin.Endocrinol.Diabetes* 113 (9):545-550, 2005.	Wrong follow-up: only 7 days. Wrong outcomes.
BUYSSCHAERT 1987 M. Buysschaert, P. Minette, and J. M. Ketelslegers. Comparison of blood glucose profile and glycemic control in type 1 diabetic patients treated with actrapid-monotard or actrapid protaphane (NPH) human insulins. *DIABETES RES.* 4 (1):31-33, 1987.	Wrong analysis/subgroups for outcomes: HbA1c results given, but these are given only for subgroups of C-peptide negative pts and for those with residual insulin secretion.
VELASQUEZ 2008 PA. Velasquez-Mieyer and CP. Neira. Biphasic insulin aspart 30 for the treatment of type 1 diabetes mellitus. *Expert Opin.Pharmacother.* 9 (13):2377-2382, 2008.	SR – used as source of references
CORCORAN 1986 J. S. Corcoran and J. S. Yudkin. A comparison of premixed with patient-mixed insulins. *Diabet.Med.* 3 (3):246-249, 1986.	Wrong population: does not mention the type of diabetes, just 'diabetes'.
SEGAL 2013 D. Segal, D. Tupy, and L. Distiller. The biosulin equivalence in standard therapy (BEST) study - A multicentre, open-label, non-randomised, interventional, observational study in subjects using Biosulin 30/70 for the treatment of insulin-dependent type 1 and type 2 diabetes mellitus. *S.Afr.Med.J.* 103 (7):458-460, 2013.	Not an RCT.
PIEBER 2013A T. Pieber, S. Korsatko, S. Deller, H. Kojzar, C. Roepstorff, A. L. Svendsen, and H. Haahr. The distinct prandial and basal pharmacodynamics of IDegAsp observed in younger adults are preserved in elderly subjects with type 1 diabetes. *Diabetes* 62:A237, 2013.	Conference abstract. Single dose study – not treatment over time.
HEISE 2013 T. Heise, L. Nosek, O. Klein, H.-V. Coester, C. Roepstorff, svendsen A. Louise, and H. Haahr. IDegAsp produces dose-proportional glucose-lowering effect in subjects with type 1 diabetes. *Diabetes* 62:A241, 2013.	Conference abstract. Single dose study – not treatment over time.
CENGIZ 2012 E. Cengiz, K. L. Swan, W. V. Tamborlane, J. L. Sherr, M. Martin, and S. A. Weinzimer. The alteration of aspart insulin pharmacodynamics when mixed with detemir insulin. *Diabetes care* 35 (4):690-692, 2012.	Already found this study in pre-rerun literature. Was excluded due to wrong follow-up: only 300 mins.
HIRSCH 2012B I. B. Hirsch, B. Bode, J. P. Courreges, P. Dykiel, E. Franek, K. Hermansen, A. King, H. Mersebach, and M. Davies. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal-bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. *Diabetes care* 35 (11):2174-2181, 2012.	Already found this study in pre-rerun literature. Was included in evidence review.
MA 2012	Already found this study in pre-rerun literature. Was

Reference	Reason for exclusion
Z. Ma, T. Parkner, J. Frystyk, T. Laursen, T. Lauritzen, and J. S. Christiansen. A comparison of pharmacokinetics and pharmacodynamics of insulin aspart, biphasic insulin aspart 70, biphasic insulin aspart 50, and human insulin: a randomized, quadruple crossover study. *Diabetes technology and therapeutics* 14 (7):589-595, 2012.	excluded due to wrong follow-up: only 720 hours.
MA 2014 Z Ma, JS Christiansen, T Laursen, C Wu, T Lauritzen, T Parkner, and J Frystyk. Effects of human insulin and insulin aspart preparations on levels of IGF-I, IGFBPs and IGF bioactivity in patients with type 1 diabetes. *BMC Endocr Disord* 14 (1):35, 2014.	Ordered for SA insulin question and was excluded due to wrong follow-up time.
NOSEK 2013 L. Nosek, T. Heise, O. Klein, H.-V. Coester, C. Roepstorff, A. Svendsen, and H. Haahr. IDegAsp produces a dose-proportional glucose-lowering effect in subjects with type 1 diabetes. *Diabetologia* 56:S418-S419, 2013.	Conference abstract
TESTA 2012 M. A. Testa, J. Gill, M. Su, R. R. Turner, L. Blonde, and D. C. Simonson. Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. *Journal of clinical endocrinology and metabolism* 97 (10):3504-3514, 2012.	Already found this study in pre-rerun literature. Was included in evidence review.
Additional studies from old GL, TA and cross-referencing SRs, MAs and other GLs	
GAO 2008 Y. Gao, G. Li, Y. Li, X. Guo, G. Yuan, Q. Gong, L. Yan, Y. Zheng, and J. Zhang. Postprandial blood glucose response to a standard test meal in insulin-requiring patients with diabetes treated with insulin lispro mix 50 or human insulin mix 50. *Int.J.Clin.Pract.* 62 (9):1344-1351, 2008.	Wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis, and only 10% are type 1 diabetes.

K.4.4 Adjuncts

Reference	Title	Reason for exclusion
Amiel 2005[34]	The effect of pramlintide on hormonal, metabolic or symptomatic responses to insulin-induced hypoglycaemia in patients with type 1 diabetes	Outcomes not relevant
Ceriello 2005[81]	Effects of pramlintide on postprandial glucose excursions and measures of oxidative stress in patients with type 1 diabetes	Follow-up only 1 day
Fang 2013[144]	Study reanalysis using a mechanism-based pharmacokinetic/pharmacodynamic model of pramlintide in subjects with type 1 diabetes	Age group mixed or unclear
Fineman 2002[149]	The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes	Wrong outcomes
Gin 1985[169]	Metformin improved insulin resistance in type I, insulin-dependent, diabetic patients	Wrong outcomes
Gomez 2002[177]	Metformin adjunctive therapy with insulin improves glycemic control in patients with type 1 diabetes mellitus: a pilot study	Age group mixed or unclear
Higginbotham 1979[210]	Double-blind trial of metformin in the therapy of non-ketotic diabetics	Not guideline condition, Not review population, Mixed population: type 1 diabetes and type 2 diabetes with no type 1

Reference	Title	Reason for exclusion
		diabetes subgroup analysis
Janssen 1991[233]	Effects of metformin on haemorheology, lipid parameters and insulin resistance in insulin-dependent diabetic patients (IDDM)	Not an RCT
Kong 1997[264]	Infusion of pramlintide, a human amylin analogue, delays gastric emptying in men with IDDM	Follow-up only 4 hours
Kong 1998 [265]		Follow-up only 1 day
Kuhadiya 2012[269]	Long-term follow-up of patients with type 1 diabetes on liraglutide and the effect of liraglutide as additional treatment in obese patients with type 1 diabetes	Not an RCT, Conference abstract of a study that is not an RCT
Lamanna 2011[275]	Effect of metformin on cardiovascular events and mortality: A meta-analysis of randomized clinical trials	SR of studies in type 2 diabetes
Lee 2010[282]	Efficacy and harms of the hypoglycemic agent pramlintide in diabetes mellitus	Systematic review: used for references
Levetan 2003[291]	Impact of pramlintide on glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps	Age group mixed or unclear
Lund 2009[298]	Effect of adjunct metformin treatment on levels of plasma lipids in patients with type 1 diabetes	Wrong outcomes
Meneilly 2003[327]	Effect of glucagon-like peptide 1 (7-36 amide) on insulin-mediated glucose uptake in patients with type 1 diabetes	Incorrect interventions, Inappropriate comparison
Moon 2007[340]	The addition of metformin in type 1 diabetes improves insulin sensitivity, diabetic control, body composition and patient well-being	Not an RCT
Nogid 2006[373]	Adjunctive therapy with pramlintide in patients with type 1 or type 2 diabetes mellitus	Systematic review: used for references
Noto 2011[375]	Significantly decreased risk of cancer in patients with diabetes mellitus on metformin: A systematic review and meta-analysis	Conference abstract of a systematic review
Nyholm 1996[376]	Acute effects of the human amylin analog AC137 on basal and insulin- stimulated euglycemic and hypoglycemic fuel metabolism in patients with insulin-dependent diabetes mellitus	Wrong outcomes
Orskov 1999[383]	Effects of the amylin analogue pramlintide on hepatic glucagon responses and intermediary metabolism in Type 1 diabetic subjects	Wrong outcomes
Pagano 1983[387]	Metformin reduces insulin requirement in Type 1 (insulin-dependent) diabetes	Not an RCT
Ramchandani 2012[414]	Closed loop system in conjunction with pramlintide and exenatide improves post-prandial hyperglycemia	Wrong intervention/comparison: closed loop system with placebo, pramlintide or exenatide, Only 1 week follow-up
Ratner 2005[418]	Adjunctive therapy with pramlintide lowers HbA1c without concomitant weight gain and increased risk of severe hypoglycemia in patients with type 1 diabetes approaching glycemic targets	Systematic review: used for references
Rizkalla 1986[432]	Effects of metformin treatment on erythrocyte insulin binding in normal weight subjects, in obese non diabetic subjects, in type 1 and type 2 diabetic	Age group mixed or unclear

Reference	Title	Reason for exclusion
	patients	
Samsom 2000[444]	Pramlintide, an amylin analog, selectively delays gastric emptying: potential role of vagal inhibition	Healthy population
Singh 2012[465]	Metformin and risk of pancreatic cancer in patients with diabetes mellitus: A systematic review and meta-analysis	Conference abstract of a systematic review
Vella 2010[508]	The use of metformin in type 1 diabetes: a systematic review of efficacy	Systematic review: used for references
Wang 2012[512]	Diabetes mellitus and risk of hepatocellular carcinoma: A systematic review and meta-analysis	Systematic review: used for references
Weinzimer 2012[515]	Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes	Follow-up only 2 days
Weyer 2003 [518]		Follow-up only 1 day
Younk 2011[534]	Pramlintide and the treatment of diabetes: A review of the data since its introduction	Systematic review: used for references
HERRMANN 2013	K Herrmann, JP. Frias, SV. Edelman, K Lutz, K Shan, S Chen, D Maggs, and OG. Kolterman. Pramlintide improved measures of glycemic control and body weight in patients with type 1 diabetes mellitus undergoing continuous subcutaneous insulin infusion therapy. *Postgrad.Med.* 125 (3):136-144, 2013.	Post-hoc analysis of 2 x RCTs (one in type 2 diabetes and the other in type 1 diabetes which we have already got in our review).
HERRMANN 2013A	K. Herrmann, S. C. Brunell, K. Shan, and S. Chen. Effects of pramlintide on A1C, weight, and hypoglycemia in patients with type 1 or type 2 diabetes: Subgroup analysis by duration of diabetes. *Diabetes* 62:A267, 2013.	Conference abstract – already have enough fully published evidence for this question.
HELLER 2013	S. R. Heller, S. Korsatko, J. Gurban, L. Jensen, E. Christiansen, F. Kiyomi, and T. R. Pieber. Liraglutide as adjunct to insulin in type 1 diabetes: Effects on glycemic control and safety in a randomized, double-blind, crossover trial. *Diabetes* 62:A258-A259, 2013.	Conference abstract – already have enough fully published evidence for this question.
PIEBER 2013	T. Pieber, S. Deller, M. Brunner, L. Jensen, E. Christiansen, F. Kiyomi, and S. Heller. Effects of liraglutide as adjunct to insulin on counter-regulatory hormone responses to hypoglycemia in type 1 diabetes: A randomized, double-blind, crossover trial. *Diabetes* 62:A258, 2013.	Conference abstract – already have enough fully published evidence for this question.
WANG 2013A	B. Wang, J. Zhong, H. Lin, Z. Zhao, Z. Yan, H. He, Y. Ni, D. Liu, and Z. Zhu. Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials. *Diabetes Obesity and Metabolism* 15 (8):737-749, 2013.	SR/MA but studies included are wrong population: type 2 diabetes studies
WEINZIMER 2012	S. A. Weinzimer, J. L. Sherr, E. Cengiz, G. Kim, J. L. Ruiz, L. Carria, G. Voskanyan, A. Roy, and W. V. Tamborlane. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. *Diabetes Care* 35 (10):1994-1999, 2012.	Wrong population: mix of adults and young people, with no adult subgroup analysis and % of adults not reported. Closed loop study, not treatment over tme.
HAMAMOTO 2013	Y. Hamamoto, S. Honjo, Y. Kawasaki-Ogita, H. Tatsuoka, K. Fujimoto, A. Matsuoka, H. Ikeda, Y. Wada, and H. Koshiyama. Long-term effects of liraglutide on pancreatic beta cell function and	Conference abstract

Reference	Title	Reason for exclusion
	glycaemic control in type 1 diabetes with residual insulin secretion. *Diabetologia* 56:S351-S352, 2013.	
HELLER 2013	S. R. Heller, S. Korsatko, J. Gurban, L. Jensen, E. Christiansen, F. Kiyomi, and T. R. Pieber. Positive effects of liraglutide as adjunct to insulin in type 1 diabetes: Glycaemic control and safety in a randomised, double blind, placebo controlled crossover trial. *Diabetologia* 56:S7-S8, 2013.	Conference abstract
KLIM 2013	S. Klim, S. H. Ingwersen, L. Jensen, F. Kiyomi, J. Mader, S. Heller, and T. R. Pieber. Liraglutide demonstrates similar pharmacokinetic properties in patients with type 1 and type 2 diabetes. *Diabetologia* 56:S404, 2013.	Conference abstract
KUHADAYA 2014	N. D. Kuhadiya, S. Dhindsa, A. Makdissi, H. A. Ghanim, M. Batra, A. Chaudhuri, J. Hejna, K. Green, N. Bellini, and P. Dandona. Liraglutide as additional treatment to insulin in patients with type 1 diabetes mellitus: A randomized clinical trial. *Diabetes* 63:A250, 2014.	Conference abstract
KUMAR 2014	A. Kumar. Insulin degludec/liraglutide: Innovation-driven combination for advancement in diabetes therapy. *Expert Opin.Biol.Ther.* 14 (6):869-878, 2014.	SR – used as source of references.
PIEBER 2013	T. R. Pieber, S. Deller, M. Brunner, L. Jensen, E. Christiansen, F. Kiyomi, and S. R. Heller. Treatment with liraglutide as adjunct to insulin in type 1 diabetes; Effects on counter regulatory response to hypoglycaemia: A randomised, double blind, crossover trial. *Diabetologia* 56:S404-S405, 2013.	Conference abstract
RAMCHANDANI 2014	N. Ramchandani, J. Trast, V. S. Renukuntla, D. Johnson-Newell, G. Dinapoli, M. Cantwell, and R. A. Heptulla. Liraglutide in the closed-loop system lowers postprandial hyperglycemia. *Diabetes* 63:A244, 2014.	Conference abstract
RAMKISSOON 2014	C. M. Ramkissoon, B. Aufderheide, B. W. Bequette, and C. C. Palerm. A model of glucose-insulin-pramlintide pharmacokinetics and pharmacodynamics in type 1 diabetes. *J.Diabetes Sci.Technol.* 8 (3):529-542, 2014.	Unable to obtain article. Wrong outcome measures (not clinical).
SMILEY 2014	D. Smiley, I. Anzola, W. Duan, M. Hudson, L. Zhao, and G. E. Umpierrez. Long-term effects of metformin and sitagliptin on near-normoglycemic remission, beta-cell function, and insulin sensitivity in obese African Americans with hyperglycemic crises. *Diabetes* 63:A40, 2014.	Conference abstract

K.4.5 Needle length, site, rotation

Reference	Reason for exclusion
MIWA 2012 T. Miwa, R. Itoh, T. Kobayashi, T. Tanabe, J. Shikuma, T. Takahashi, and M. Odawara. Comparison of the effects of a new 32-Gaugex4-mm pen needle and a 32-Gaugex6-mm pen needle on glycemic control, safety, and patient ratings in japanese adults with diabetes. *Diabetes Technol.Ther.* 14 (12):1084-1090, 2012.	Already included in original evidence review

Reference	Reason for exclusion
MCVEY 2012 E McVey, Laurence Hirsch, Diane E. Sutter, Christoph Kapitza, Sibylle Dellweg, Janina Clair, Kerstin Rebrin, Kevin Judge, and Ronald J. Pettis. Pharmacokinetics and postprandial glycemic excursions following insulin lispro delivered by intradermal microneedle or subcutaneous infusion. *J Diabetes Sci Technol* 6 (4):743-754, 2012.	Wrong comparison: microneedle vs. sc infusion (not injection)
MCVEY 2014 E. Mcvey, D. Sutter, C. Rini, L. Nosek, C. Kapitza, K. Rebrin, and R. Pettis. Intradermal insulin infusion achieves faster insulin action than subcutaneous infusion for three day wear. *Diabetes Technol.Ther.* 16:A27-A28, 2014.	Conference abstract
WONG 2013 M Wong, Radhi Abdulnabi, and Haoda Fu. Ease of use of two reusable, half-unit increment dosing insulin pens by adult caregivers of children with type 1 diabetes: a randomized, crossover comparison. *J Diabetes Sci Technol* 7 (2):582-583, 2013.	Children.
WONG 2013A M Wong, Radhi Abdulnabi, Michelle A. Carey, and Haoda Fu. A randomized, cross-over comparison of preference between two reusable insulin pen devices in pen-naive adults with diabetes. *Curr.Med.Res.Opin.* 29 (5):465-473, 2013.	Does not answer the question. Ease of use of different pen designs, not different needles.
KREUGEL 2013 Randomized trial on the influence of the length of two insulin pen needles on glycemic control and patient preference in obese patients with diabetes.	Conference abstract. Full study was published in 2011 and has been used in our original review.
SOMMAVILLA 2013 A randomized, open-label, comparative crossover handling trial between two durable pens in patients with type 1 or 2 diabetes mellitus.	Conference abstract. Full study was published in 2011 and has been used in our original review.
IGNAUT 2012 D. A. Ignaut and H. Fu. Comparison of insulin diluent leakage postinjection using two different needle lengths and injection volumes in obese patients with type 1 or type 2 diabetes mellitus. *J Diabetes Sci Technol* 6 (2):389-393, 2012.	Already included in original evidence review
MIWA 2012 T. Miwa, R. Itoh, T. Kobayashi, T. Tanabe, J. Shikuma, T. Takahashi, and M. Odawara. Comparison of the effects of a new 32-Gaugex4-mm pen needle and a 32-Gaugex6-mm pen needle on glycemic control, safety, and patient ratings in japanese adults with diabetes. *Diabetes Technol.Ther.* 14 (12):1084-1090, 2012.	Already included in original evidence review

K.5 Pancreas transplant and islet cell transplantation

None

K.6 Hypoglycaemia

K.6.1 Identification and quantification of impaired awareness of hypoglycaemia

Reference	Reason for exclusion
AMIEL 2011 Amiel SA. Using the brain to reduce hypoglycaemia. Diabetes Technology and Therapeutics. 2011; 13(2):174.	Conference abstract of an oral presentation. Does not answer the question – shows effect of intervention at restoring hypo awareness.
BOLLI 1999 Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. Diabetes Care. 1999; 22 Suppl 2:B43-B52.	Review article. Does not answer the question – shows effect of intervention at restoring hypo awareness.
CHOUDHARY 2011A Choudhary P, Thomakos P, Pernet A, Wilson B, Hopkins D, Amiel SA. Reduced hypoglycaemia burden after three months of continuous glucose monitoring in patients with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabetic Medicine. 2011; 28:144.	Conference abstract. Does not answer the question – shows effect of intervention at restoring hypo awareness.
CHOUDHARY 2011B Choudhary P, Thomakos P, Wilson B, Pernet A, Hopkins D, Amiel SA. Reduction of hypoglycemia burden following three months of continuous glucose monitoring in patients with impaired awareness of hypoglycemia. Diabetes. 2011; 60:A138.	Conference abstract. Does not answer the question – shows effect of intervention at restoring hypo awareness.
CONGET 2009 Conget I, Lara M, Mora M, Gimenez M. Improvement in hypoglycaemia awareness and amelioration if glycaemic profile using CSII in type 1 diabetic subjects with repeated severe hypoglycaemia. Diabetologia. 2009; 52(S1):S234.	Conference abstract. Does not answer the question – shows effect of intervention at restoring hypo awareness.
DEGALAN 2006 de Galan BE, Schouwenberg BJJW, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. Netherlands Journal of Medicine. 2006; 64(8):269-279.	Review article, used for references.
HOPKINS 2012 D. Hopkins, I. Lawrence, P. Mansell, G. Thompson, S. Amiel, M. Campbell, and S. Heller. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care* 35 (8):1638-1642, 2012.	Does not answer the question – shows effect of DAFNE education intervention at restoring hypo awareness.

Reference	Reason for exclusion
KOVATCHEV 2011 Kovatchev BP, Mendosa P, Anderson S, Hawley JS, Ritterband LM, Gonder-Frederick L. Effect of automated bio-behavioral feedback on the control of type 1 diabetes. Diabetes Care. 2011; 34(2):302-307.	Does not answer the question – shows effect of intervention at restoring hypo awareness.
LEELARATHNA 2013C Leelarathna L, Little SA, Walkinshaw E, Tan HK, Kumareswaran K, Lubina SA et al. Patients with longstanding type 1 diabetes show improved self awareness of hypoglycaemia measured during clamped hypoglycaemic challenges after a six month intensive treatment period in the HypoCOMPASS Study: Comparison of optimised multiple daily injections (MDI) and continuous insulin infusion therapy (CSII) with or without adjunctive real-time continuous glucose monitoring (RTCGM). Diabetic Medicine. 2013; 30:14.	Conference abstract. Does not answer the question – shows effect of intervention at restoring hypo awareness.
MACLEOD 1994 K. M. MacLeod, I. J. Deary, K. S. Graham, D. A. Hepburn, and B. M. Frier. Hypoglycaemia unawareness in adult patients with Type I diabetes: Relationship to severe hypoglycaemia and cognitive impairment. *Diabetes Nutr.Metab.Clin.Exp.* 7 (4):205-212, 1994.	Cognitive impairment related to history of hypo unawareness.
MATEJKO 2013 Matejko B, Grzanka M, Kiec-Wilk B, Malecki MT, Klupa T. Clinical factors affecting the perception of hypoglycemia in type 1 diabetes patients treated with personal insulin pumps. Annals of Agricultural and Environmental Medicine. 2013; 20(1):152-154.	Correlation between hypoglycaemia perception and severe hypoglycaemia in CSII patients, but does not give any details of the questionnaire that was used to define hypo unawareness.
MULHAUSER 1998 I. Muhlhauser, H. Overmann, R. Bender, U. Bott, and M. Berger. Risk factors of severe hypoglycaemia in adult patients with Type I diabetes--a prospective population based study. *Diabetologia* 41 (11):1274-1282, 1998.	Risk factors for severe hypo. Includes hypo unawareness. Does not look at risks for hypo unawareness or use of score for identification.
PEDERSEN 2009A Pedersen-Bjergaard U. Severe hypoglycaemia in type 1 diabetes: impact of the renin-angiotensin system and other risk factors. Danish Medical Bulletin. 2009; 56(4):193-207.	Review article, used for references.
RYAN 2005 E. A. Ryan, B. W. Paty, P. A. Senior, J. R. Lakey, D. Bigam, and A. M. Shapiro. Beta-score: an assessment of beta-cell function after islet transplantation. *Diabetes Care* 28 (2):343-347, 2005.	Score assesses beta-cell function not impaired awareness of hypoglycaemia (IAH).
RYAN 2005A E. A. Ryan, B. W. Paty, P. A. Senior, D. Bigam, E. Alfadhli, N. M. Kneteman, J. R. Lakey, and A. M. Shapiro. Five-year follow-up after clinical islet transplantation. *Diabetes* 54 (7):2060-2069, 2005.	Effect of treatment on IAH, does not look at ability of score to identify IAH pts.

Reference	Reason for exclusion
SEJLING 2012 A.-S. Sejling, B. Thorsteinsson, and U. Pedersen-Bjergaard. The effect of mild and severe hypoglycaemia and hypoglycaemia awareness on 12-year all-cause mortality in type 1 diabetes. *Diabetologia* 55:S98, 2012.	Effect of hypo unawareness on mortality. Does not show risks for hypo unawareness or look at methods of identification.
TAHIR 2003 M. Tahir and N. H. Patel. Quality of life scores, treatment satisfaction scores and hypoglycaemia awareness scores are more valid measures of the impact of continuous subcutaneous insulin infusion (CSII) initiation than HbA1c in patients with Type 1 diabetes. *Diabet.Med.* 30:199, 2013.	Conference abstract. Does not look at the ability of Clarke score to identify hypo unaware/impaired hypo awareness pts. Looks at effect of treatment on improving Clarke score (ie. recovering impaired hypo awareness).
LY 2013 T. T. Ly, J. A. Nicholas, A. Retterath, E. M. Lim, E. A. Davis, and T. W. Jones. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 310 (12):1240-1247, 2013.	Mixed population: adults, children, young people. <50% adults (approx.. 30%) and no adult subgroup analysis.
GARG 2014 Change in a1c and reduction in hypoglycemia with threshold suspend in the aspire in-home study. Diabetes technology and therapeutics: 16: A107. Garg SK, Weiss R, Shah A, Mao M, and Kaufman FR. 2014	Conference abstract.
DASKALAKI2013. Alarm system for the early warning of hypo- and hyperglycemic events based on online adaptive models. Diabetes technology and therapeutics: 15: A77-A78. Daskalaki E, Norgaard K, Prountzou A, Zuger T, Diem P, and Mougiakakou S. 2013	Conference abstract. Validation/accuracy study.
DEZOYSA2013 Tackling intractable problematic hypoglycemia in type 1 diabetes: the dafne-hart pilot study. Diabetes: 62: A65. Dezoysa N, Rogers H, Beveridge S, Gianfrancesco C, Choudhary P, Elliott J, Heller SR, and Amiel SA. 2013	Conference abstract. Already included full study in the review (epublished ahead of print – DEZOYSA 2014)
HOLMESWALKER2013 Islet transplantation prevents severe hypoglycemia more effectively than continuous subcutaneous insulin infusion (CSII). Diabetes: 62: A34. Holmes-Walker J, Gunton J, Ward G, Kay T, and O'connell P. 2013	Conference abstract.
LITTLE 2013 A definitive multicenter rct to restore hypoglycemia awareness and prevent recurrent severe hypoglycemia in adults with long- standing type 1 diabetes: Results from the hypocompass trial. Diabetes: 62: A98. Little SA, Leelarathna L, Walkinshaw E, Kai TH, Chapple O, Solomon AL, Barendse S,	Conference abstract.

Reference	Reason for exclusion
Chadwick T, Brennand C, Stocken D, Wood R, Marshall SM, Begley J, Kerr D, Speight J, Flanagan D, Heller SR, Evans ML, and Shaw JAM. 2013	
ADAMSON 2013 K. A. Adamson, M. Hassanein, I. Malik, H. White, and J. Vora. Short or intermittent use of continuous glucose monitoring (CGM) enhances glycaemic control in subjects with persistently poorly controlled diabetes. *Diabet Med* 30:160, 2013.	Conference abstract
ANDERSON 2010A P. F. Anderson. Quality of life (QOL) in patients with severe hypoglycaemia unawareness before and after islet transplantation. *Transplantation* 90:1017, 2010.	Conference abstract
BJORGAAS 2013 M. R. Bjorgaas, S. E. Olsen, B. M. Frier, and B. O. Asvold. The effects of diabetes duration on hypoglycemia symptom intensity and prevalence of impaired awareness of hypoglycemia. *Pediatr.Diabetes* 14:70-71, 2013.	Conference abstract
CHOUDHARY 2013A P. Choudhary, S. Ramasamy, G. Gallen, L. Green, J. Pickup, and S. Amiel. Reduction in severe hypoglycaemia with the use of continuous glucose monitoring in clinical practice. *Diabet Med* 30:147-148, 2013.	Conference abstract
CHOUDHARY 2014 P. Choudhary, J. Dunn, Teh M. Ming, A. Pernet, B. M. Wilson, L. J. Reed, P. K. Marsden, and S. A. Amiel. Regional brain responses to hypoglycemia in type 1 diabetes: Impact of hypoglycemia awareness status. *Diabetes* 63:A101, 2014.	Conference abstract
CZYZEWSKA 2013 K. Czyzewska and A. Szadkowska. Hypoglycemia awareness training in type 1 diabetic patients with hypoglycemia unawareness. *Pediatr.Diabetes* 14:19, 2013.	Conference abstract
DAVENPORT 2013 K. Davenport, S. Ng, J. Chen, T. Ebsworth, C. Ward, and M. L. Evans. Reduced fear of hypoglycaemia with continuous subcutaneous insulin infusion (CSII) therapy in people with Type 1 diabetes. *Diabet Med* 30:147, 2013.	Conference abstract
DE 2014 DeZoysa N. de, H. Rogers, M. Stadler, C. Gianfrancesco, S. Beveridge, E. Britneff, P. Choudhary, J. Elliott, S. Heller, and S. A. Amiel. A psychoeducational program to restore hypoglycemia awareness: The DAFNE-HART pilot study. *Diabetes care* 37 (3):863-866, 2014.	Already included full study in the review (epublished ahead of print – DEZOYSA 2014)

Reference	Reason for exclusion
DESJARDINS 2014 K. Desjardins, A. S. Brazeau, I. Strychar, and R. Rabasa-Lhoret. Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes? *Diabetes Obes Metab* 16 (7):577-587, 2014.	SR – used as source of references.
DEZOYSA 2013 N. DeZoysa, H. Rogers, C. Gianfrancesco, S. Beveridge, V. Francis, J. Elliott, P. Choudhary, S. Heller, and S. A. Amiel. A psychological intervention for tackling intractable hypoglycaemia in patients with Type 1 diabetes: The pilot study Dose Adjustment for Normal Eating Hypoglycaemia Awareness Restoration Trial (DAFNE-HART). *Diabet Med* 30:148, 2013.	Conference abstract. Already included full study in the review (epublished ahead of print – DEZOYSA 2014)
GANDHI 2013 K. Gandhi, S. S. Hussain, E. Charatsi, and A. Dornhorst. Investigating hypoglycaemia awareness in an outpatient Type 1 diabetes clinic. *Diabet Med* 30:148, 2013.	Conference abstract
HENRIKSEN 2013 M. M. Henriksen, R. Due-Andersen, B. Thorsteinsson, and U. Pedersen-Bjergaard. Recurrent severe hypoglycaemia in type 1 diabetes: Potential for prevention? *Diabetologia* 56:S423, 2013.	Conference abstract
HERING 2014 B. J. Hering, N. D. Bridges, T. L. Eggerman, and W. R. Clarke. Phase 3 trial of transplantation of human islets in type 1 diabetes (T1D) complicated by severe hypoglycemia. *Diabetes* 63:A102, 2014.	Conference abstract
HUSSAIN 2014 S. S. Hussain, K. Ghandi, and A. Dornhorst. A comparison of methods used to assess impaired awareness of hypoglycaemia in Type 1 Diabetes. *Diabet Med* 31:129, 2014.	Conference abstract
JENSEN 2013 M. H. Jensen, T. F. Christensen, L. Tarnow, Z. Mahmoudi, M. D. Johansen, and O. K. Hejlesen. Professional continuous glucose monitoring in subjects with type 1 diabetes: Retrospective hypoglycemia detection. *J.Diabetes Sci.Technol.* 7 (1):135-143, 2013.	Ordered for CGM question.
JENSEN 2014 M. H. Jensen, Z. Mahmoudi, T. F. Christensen, L. Tarnow, E. Seto, M. D. Johansen, and O. K. Hejlesen. Evaluation of an algorithm for retrospective hypoglycemia detection using professional continuous glucose monitoring data. *J.Diabetes Sci.Technol.* 8 (1):117-122, 2014.	Wrong population: only 30% IAH.

Reference	Reason for exclusion
KOEHLER 2014A G Koehler, S Heller, S Korsatko, C Roepstorff, S Rasmussen, H Haahr, and TR. Pieber. Insulin degludec is not associated with a delayed or diminished response to hypoglycaemia compared with insulin glargine in type 1 diabetes: a double-blind randomised crossover study. *Diabetologia* 57 (1):40-49, 2014.	Ordered for LA insulin question.
LEELARATHNA 2013A L. Leelarathna, S. A. Little, E. Walkinshaw, H. K. Tan, A. Lubina-Solomon, K. Kumareswaran, A. P. Lane, T. Chadwick, S. M. Marshall, J. Speight, D. Flanagan, S. R. Heller, J. A. M. Shaw, and M. L. Evans. Restoration of self-awareness of hypoglycemia in adultswith long-standing type 1 diabetes: Hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. *Diabetes care* 36 (12):4063-4070, 2013.	Conference abstract
LEELARATHNA 2013C L. Leelarathna, S. A. Little, E. Walkinshaw, H. K. Tan, K. Kumareswaran, Solomon A. Lubina, D. Flanagan, S. Heller, J. A. M. Shaw, M. L. Evans, and E. Chow. Patients with longstanding type 1 diabetes show improved self awareness of hypoglycaemia measured during clamped hypoglycaemic challenges after a six month intensive treatment period in the HypoCOMPASS Study: Comparison of optimised multiple daily injections (MDI) and continuous insulin infusion therapy (CSII) with or without adjunctive real-time continuous glucose monitoring (RTCGM). *Diabet Med* 30:14, 2013.	Study already found in pre-rerun literature. Was excluded as conference abstract. Fully published version has been included in evidence (LITTLE 2012).
LEWIS 2014 K. Lewis, S. Mccrone, S. Bendre, P. Deiriggi, and A. Dye. Effectiveness of continuous glucose monitoring in children, adolescents, and young adults with poorly controlled type 1 diabetes. *Diabetes* 63:A218, 2014.	Conference abstract
LITTLE 2014 SA. Little, L Leelarathna, E Walkinshaw, H Tan, O Chapple, A Lubina-Solomon, TJ. Chadwick, S Barendse, DD. Stocken, C Brennand, SM. Marshall, et al. Recovery of Hypoglycemia Awareness in Long-standing Type 1 Diabetes: A Multicenter 2 x 2 Factorial Randomized Controlled Trial Comparing Insulin Pump With Multiple Daily Injections and Continuous With Conventional Glucose Self-monitoring (HypoCOMPaSS). *Diabetes care* 37 (8):2114-2122, 2014.	Compares CGM vs. SMBG in patioents with IAH Could use data from the CGM arm? If pts wre previously using SMBG only. No relevant outcomes – protocol (LITTLE 2012) was excluded pre-reruns as does not match protocol.
LITTLE 2012 S. Little, T. Chadwick, P. Choudhary, C. Brennand, J. Stickland, S. Barendse, T. Olateju, L. Leelarathna, E. Walkinshaw, H. K. Tan, S. M. Marshall, R. M. Thomas, S. Heller, M. Evans, D.	Already found study in pre-rerun evidence. Study was excluded from the review due to being a study protocol and worng outcome measures.

Reference	Reason for exclusion
Kerr, D. Flanagan, J. Speight, and J. A. M. Shaw. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). *BMC endocrine disorders* 12, 2012.	
MOHEET 2014 A. Moheet, S. Mangia, A. Kumar, N. Tesfaye, L. E. Eberly, Y. Bai, and E. R. Seaquist. Naltrexone for treatment of hypoglycemia unawareness in type 1 diabetes: A randomized clinical trial. *Diabetes* 63:A103, 2014.	Conference abstract
PEDERSEN 2013 U. Pedersen-Bjergaard, P. L. Kristensen, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, P. Hougaard, H.-H. Parving, B. Thorsteinsson, and L. Tarnow. The effect on insulin analogues on the risk of severe hypoglycaemia in patients with type 1 diabetes and recurrent severe hypoglycaemia: The HypoAna trial. *Diabetologia* 56:S84, 2013.	Conference abstract
PEDERSEN 2014A U. Pedersen-Bjergaard, P. L. Kristensen, H. Beck-Nielsen, K. Norgaard, H. Perrild, J. S. Christiansen, T. Jensen, P. Hougaard, H.-H. Parving, B. Thorsteinsson, and L. Tarnow. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): A prospective, randomised, open-label, blinded-endpoint crossover trial. *Lancet Diabetes Endocrinol.* 2 (7):553-561, 2014.	Wrong population: type 1 diabetes but do not have impaired awareness
PEREZMARAVER 2013 M. Perez-Maraver, J. Caballero-Corchuelo, A. Boltana, R. Insa, J. Soler, and E. Montanya. Comparison of human insulin and insulin analogues on hypoglycaemia and metabolic variability in type 1 diabetes using standardized measurements (HYPO score and Lability Index). *Acta Diabetol* 50 (4):529-535, 2013.	SR – used as source of refernces.
POOLSUP 2013 N Poolsup, Suksomboon, and A M Kyaw. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndr* 5:39, 2013.	Ordered for CGM question and excluded due to wrong populations in the studies.
RAY 2013B T. Ray, P. Choudhary, P. Mansell, S. Heller, S. A. Amiel, and D. Hopkins. Dose Adjustment for Normal Eating (DAFNE) structured education is associated with reduced progression to insulin pump among patients considered for pump before enrolment. *Diabetologia* 56:S444, 2013.	Conference abstract
RAY 2013A T. Ray, P. Choudhary, P. Mansell, S. Heller, S. A. Amiel, and D. Hopkins. Dose adjustment for normal eating (DAFNE)	Conference abstract

Reference	Reason for exclusion
structured education reduces progression to continuous subcutaneous insulin infusion (CSII) among patients being considered for insulin pump therapy at enrolment. *Diabet Med* 30:7-8, 2013.	
RUSSELLJONES 2013 D. L. Russell-Jones, S. Heller, C. T. Hansen, D. Chang, and B. Bode. A two year randomised trial: Improved glycaemic control and lower risk of nocturnal hypoglycaemia with insulin degludec compared with insulin glargine in Type 1 diabetes. *Diabet Med* 30:74, 2013.	Conference abstract
STADLER 2014 M. Stadler, E. M. Shuttlewood, H. Rogers, C. Gianfrancesco, S. Beveridge, E. Britneff, P. Choudhary, J. Elliott, A. D. Rankin, S. A. Heller, J. Lawton, S. A. Amiel, and N. DeZoysa. DAFNE-HART, a psycho-educational programme to reverse hypoglycaemia unawareness in Type 1 diabetes: Report on sustained biomedical benefit at 1 year, and the user experience. *Diabet Med* 31:8-9, 2014.	Conference abstract
TAHIR 2013 M. Tahir and N. H. Patel. Quality of life scores, treatment satisfaction scores and hypoglycaemia awareness scores are more valid measures of the impact of continuous subcutaneous insulin infusion (CSII) initiation than HbA1c in patients with Type 1 diabetes. *Diabet Med* 30:199, 2013.	Conference abstract
TAN 2014A H. K. Tan, S. A. Little, L. Leelarathna, E. Walkinshaw, A. Lubina-Solomon, D. Kerr, S. Heller, M. L. Evans, J. A. Shaw, and D. Flanagan. Coefficient of variation from continuous glucose monitoring is associated with the frequency of hypoglycaemia in Type 1 diabetes complicated by impaired awareness of hypoglycaemia: Baseline analysis of the HypoCOMPaSS study group. *Diabet Med* 31:27, 2014.	Conference abstract

K.6.2 Recovering hypoglycaemia awareness

Reference	Reason for exclusion
ACAMPO 2010 A'Campo T, Schouwenberg B, Veldman B, Tack CJ, Smits P, de Galan BE. Prevalence and risk factors of hypoglycaemia unawareness and severe hypoglycaemia in patients with type 1 diabetes. Diabetologia. 2010; 53:S239.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
AMIEL 2011 Amiel SA. Using the brain to reduce hypoglycaemia. Diabetes Technology and Therapeutics. 2011; 13(2):174.	Conference abstract.
ANON 2004 Reigning in low blood sugar. If you're experiencing hypoglycemia without warning signs, you can train your body	Incorrect study design (letter to editor).

Reference	Reason for exclusion
to start showing them. Health News. 2004; 10(11):12.	
BOKHARI 2009 Bokhari S, Israelian Z, Emerson P, Meyer C. Improving Beta-Adrenergic sensitivity for the treatment of defective glucose counterregulation and hypoglycemia unawareness in type 1 diabetes. Diabetes. 2009; 58.	Conference abstract. Symptoms during clamps before and after 4 months treatment with propranolol in hypo unaware.
BOLLI 1998 Bolli GB. Prevention and treatment of hypoglycaemia unawareness in type 1 diabetes mellitus. Acta Diabetologica. 1998; 35(4):183-193.	Review article checked for references.
BOLLI 1999 Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. Diabetes Care. 1999; 22 Suppl 2:B43-B52.	Review article.
BOLLI 2002 Bolli GB, Pampanelli S, Porcellati F, Fanelli CG. Recovery and prevention of hypoglycaemia unawareness in type 1 diabetes mellitus. Diabetes, Nutrition and Metabolism. 2002; 15(6):402-409.	Review article checked for references.
BOLLI 2003A Bolli GB. Treatment and prevention of hypoglycemia and its unawareness in type 1 diabetes mellitus. Reviews in Endocrine and Metabolic Disorders. 2003; 4(4):335-341.	Review article.
CHALON 1999 Chalon S, Berlin I, Sachon C, Bosquet F, Grimaldi A. Propranolol in hypoglycaemia unawareness. Diabetes and Metabolism. 1999; 25(1):23-26.	Pilot study
CHANDRASEKARA 2010 Chandrasekara WMHS, Balaguruswamy S, Wessels L, Cardwell J, Wilkinson P, Hardy K et al. Dramatically reduced hypoglycaemia and restored hypoglycaemia awareness without a deterioration in HbA1c with CSII therapy. Diabetic Medicine. 2010; 27(2 SUPPL. 1):31.	Conference abstract. Population does not match protocol (not all patients had unawareness) – reported % with self-reported unawareness before and after CSII in type 1 diabetes patients.
CHOUDHARY 2010A Choudhary P, Geddes J, Freeman JV, Emery CJ, Heller SR, Frier BM. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diabetic Medicine. 2010; 27(6):666-672.	No relevant outcomes and does not match review question (frequency of severe hypoglycaemia in type 1 diabetes patients with or without impaired awareness).
CHOUDHARY 2011A Choudhary P, Thomakos P, Pernet A, Wilson B, Hopkins D, Amiel SA. Reduced hypoglycaemia burden after three months	Conference abstract. Gold score, Ryan score and blind CGM before and after 3 months treatment with CGM.

Reference	Reason for exclusion
of continuous glucose monitoring in patients with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabetic Medicine. 2011; 28:144.	
CHOUDHARY 2011B Choudhary P, Thomakos P, Wilson B, Pernet A, Hopkins D, Amiel SA. Reduction of hypoglycemia burden following three months of continuous glucose monitoring in patients with impaired awareness of hypoglycemia. Diabetes. 2011; 60:A138.	Conference abstract. Gold score, Clark score and blind CGM before and after 10 weeks treatment with CGM.
CONGET 2009 Conget I, Lara M, Mora M, Gimenez M. Improvement in hypoglycaemia awareness and amelioration if glycaemic profile using CSII in type 1 diabetic subjects with repeated severe hypoglycaemia. Diabetologia. 2009; 52(S1):S234.	Conference abstract. Clark score and SH episodes assessed before and after 6, 12 and 18 months treatment with CSII (observational before and after study).
CRYER 1998A Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Advances in Pharmacology. 1998; 42:620-622.	Review article checked for references.
CZYZEWSKA 2012 Czyzewska K, Czerniawska E, Szadkowska A. Prevalence of hypoglycemia unawareness in patients with type 1 diabetes. Pediatric Diabetes. 2012; 13:77.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in patients with type 1 diabetes).
DAGOGO 1994 Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes. 1994; 43(12):1426-1434.	Population does not match protocol – self-report of unawareness. No relevant outcomes – not enough data reported on symptoms scores
DEGALAN 2006 de Galan BE, Schouwenberg BJJW, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. Netherlands Journal of Medicine. 2006; 64(8):269-279.	Review article checked for references.
DEZOYSA 2013 DeZoysa N, Rogers H, Gianfrancesco C, Beveridge S, Francis V, Elliott J et al. A psychological intervention for tackling intractable hypoglycaemia in patients with Type 1 diabetes: The pilot study Dose Adjustment for Normal Eating Hypoglycaemia Awareness Restoration Trial (DAFNE-HART). Diabetic Medicine. 2013; 30:148.	Conference abstract. 3 month educational programme (observational before and after study). Full paper included in this review
EICHNER 1988 Eichner HL, Selam JL, Holleman CB, Worcester BR, Turner DS, Charles MA. Reduction of severe hypoglycemic events in type I (insulin dependent) diabetic patients using continuous subcutaneous insulin infusion. Diabetes Research. 1988;	Population does not match protocol (not all patients had unawareness) – incidence of SH events before and after CSII in patients with type 1 diabetes

Reference	Reason for exclusion
8(4):189-193.	
ELLIOT 2011A Elliott J, Heller S. Hypoglycaemia unawareness. Practical Diabetes International. 2011; 28(5):227-232.	Review article checked for references.
EVANS 2009 Evans ML, Hoashi S, Swamy A, Tan C-Y, Markkula SP, Roda A et al. Glucosamine improves adrenaline responses to hypoglycaemia in patients with Type 1 diabetes. Diabetic Medicine. 2009; 26:22.	Conference abstract. Intervention does not match protocol – hypoglycaemia clamp symptoms before and after single glucosamine injection
FANELLI 1995A Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Di VA, Modarelli F et al. Erratum: Long-term recovery from unawareness, deficient co;unterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM (Diabetologia Volume 37, Number 12, December 1994 (1265-1276)). Diabetologia. 1995; 38(2):254.	Book review
FANELLI 1997 Fanelli C, Pampanelli S, Lalli C, Del Sindaco P, Ciofetta M, Lepore M et al. Long-term intensive therapy of IDDM patients with clinically overt autonomic neuropathy: effects on hypoglycemia awareness and counterregulation. Diabetes. 1997; 46(7):1172-1181.	Population does not match protocol – patients with type 1 diabetes with or without diabetic autonomic neuropathy (not all had IAH)
FRITSCHE 1998 Fritsche A, Stumvoll M, Renn W, Schmulling RM. Diabetes teaching program improves glycemic control and preserves perception of hypoglycemia. Diabetes Research & Clinical Practice - Supplement. 1998; 40(2):129-135.	Intervention and population do not match protocol - structured education programme for intensification of insulin regime in type 1 diabetes (intervention not for recovery of unawareness)
GALAN 2001 Galan BE, Tack CJJ, Pasman CJW, Lutterman JA, Smits P. Theophylline imrpoves impaired hormonal and symptom responses to hypoglycemia in type 1 diabetis patients with hypoglycemia unawareness. Netherlands Journal of Medicine. 2001; 58:A13.	Conference abstract. Intervention duration does not match protocol (IV infusion of theophylline)
GALAN 2002 Galan BE, Tack CJ, Lenders JW, Pasman JW, Elving LD, Russel FG et al. Theophylline improves hypoglycemia unawareness in type 1 diabetes. Diabetes. 2002; 51(3):790-796.	Intervention duration does not match protocol (IV infusion of theophylline)
GALAN 2003 Galan BE, Tack CJ, Lenders JW, Lutterman JA, Smits P. Effect of 2 weeks of theophylline on glucose counterregulation in patients with type 1 diabetes and unawareness of hypoglycemia. Clinical Pharmacology and Therapeutics. 2003;	Intervention does not match protocol – two week duration of theophylline treatment

Reference	Reason for exclusion
74(1):77-84.	
GANDHI 2013 Gandhi K, Hussain SS, Charatsi E, Dornhorst A. Investigating hypoglycaemia awareness in an outpatient Type 1 diabetes clinic. Diabetic Medicine. 2013; 30:148.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
GEDDES 2007 Geddes J, Wright RJ, Zammitt NN, Deary IJ, Frier BM. An evaluation of methods of assessing impaired awareness of hypoglycemia in type 1 diabetes. Diabetes Care. 2007; 30(7):1868-1870.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
GEDDES 2008 Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. Diabetic Medicine. 2008; 25(4):501-504.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
GIMENEZ 2009 Gimenez M, Lara M, Jimenez A, Conget I. Glycaemic profile characteristics and frequency of impaired awareness of hypoglycaemia in subjects with T1D and repeated hypoglycaemic events. Acta Diabetologica. 2009; 46(4):291-293.	No relevant outcomes and does not match review question (prevalence of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
GLINDORF 2012 Glindorf M, Wittrup M. Effect of a 5 days intervention programme for people with type 1 diabetes and severe hypoglycaemia. Diabetologia. 2012; 55:S100-S101.	Conference abstract.
GOLD 1994 Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994; 17(7):697-703.	No relevant outcomes and does not match review question (frequency of severe hypoglycaemia in type 1 diabetes patients with or without impaired awareness).
HELLER 2010 Heller S. Hypoglycaemia in diabetes. Medicine. 2010; 38(12):671-675.	Review article
HELLER 2011B Heller SR. Hypoglycaemia: Its pathophysiology in insulin treated diabetes and hypoglycaemia unawareness. British Journal of Diabetes and Vascular Disease. 2011; 11(1):6-9.	Review article check for references
HEPBURN 1991A Hepburn DA, Frier BM. Hypoglycaemia unawareness in patients with insulin-treated diabetes mellitus. Saudi Medical Journal. 1991; 12(3):182-190.	Review article

Reference	Reason for exclusion
HERMANNS 2010 Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Long-term effect of an education program (HyPOS) on the incidence of severe hypoglycemia in patients with type 1 diabetes. Diabetes Care. 2010; 33(3):e36.	Letter to the editor. Reports outcomes from HyPOS at 31-month follow-up. Full article included in this review reporting outcomes at 6 months
HERNANDEZ 2003 Hernandez CA, Hume MR, Rodger NW. Six-month evaluation of a diabetes self-awareness intervention. Outcomes Management. 2003; 7(4):148.	Pilot study and 6 month follow-up for Hernandez 2008, included in this review
HOI-HANSEN 2010 Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. Classification of hypoglycemia awareness in people with type 1 diabetes in clinical practice. Journal of Diabetes and Its Complications. 2010; 24(6):392-397.	No relevant outcomes and does not match review question (classification and prevalence of hypoglycaemia unawareness in type 1 diabetes population and incidence of SH, no intervention).
JANSSEN 2000A Janssen MM, Snoek FJ, Heine RJ. Assessing impaired hypoglycemia awareness in type 1 diabetes: agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycemia. Diabetes Care. 2000; 23(4):529-532.	No relevant outcomes and does not match review question (classification of hypoglycaemia unawareness in type 1 diabetes population, no intervention).
JOHANSEN 2009 Johansen OE, Vanberg PJ, Kilhovd BK, Jorgensen AP. Changing basal insulin from NPH to detemir or glargine in patients with type 1 diabetes and a history of severe hypoglycemia. Vascular Health and Risk Management . 2009; 5(1):121-128.	Population does not match protocol, hypoglycaemia unawareness not mentioned - retrospective review of patients with at least one documented severe hypoglycaemia and changed from NPH to detemir or glargine
KANC 2010 Kanc K, Kastrin A, Kastrin M, Gonder-Frederick LA. Fear of hypoglycaemia - How to identify patients at risk in a routine clinical practice? Diabetologia. 2010; 53:S237-S238.	Conference abstract. No relevant outcomes and does not match review question (correlation between hypoglycaemia fear score and hypoglycaemia unawareness)
KNOTT 2012 Knott J, Ryder J, Jenkins E, Charman J, Shaban C, Cross C et al. A 12-year audit of BERTIE: Successful outcomes for at least 5 years. Diabetic Medicine. 2012; 29:20-21.	Conference abstract. Population does not match protocol
KOVATCHEV 2011 Kovatchev BP, Mendosa P, Anderson S, Hawley JS, Ritterband LM, Gonder-Frederick L. Effect of automated bio-behavioral feedback on the control of type 1 diabetes. Diabetes Care. 2011; 34(2):302-307.	Population does not match protocol – all T1d, no subgroup comparison between intervention and control for patients with HU
KUBIAK 2006A Kubiak T, Hermanns N, Schreckling HJ, Kulzer B, Haak T. Evaluation of a self-management-based patient education program for the treatment and prevention of hypoglycemia-related problems in type 1 diabetes. Patient Education and	Population does not match protocol (patients with type 1 diabetes at risk of developing hypoglycaemia-related problems but not all had hypoglycaemia problems)

Reference	Reason for exclusion
Counseling. 2006; 60(2):228-234.	
LEELARATHNA 2013C Leelarathna L, Little SA, Walkinshaw E, Tan HK, Kumareswaran K, Lubina SA et al. Patients with longstanding type 1 diabetes show improved self awareness of hypoglycaemia measured during clamped hypoglycaemic challenges after a six month intensive treatment period in the HypoCOMPASS Study: Comparison of optimised multiple daily injections (MDI) and continuous insulin infusion therapy (CSII) with or without adjunctive real-time continuous glucose monitoring (RTCGM). Diabetic Medicine. 2013; 30:14.	Conference abstract. Full paper included in this review (Little 2012)
LITTLE 2012 Little S, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S et al. Comparison of Optimised MDI versus Pumps with or without Sensors in Severe Hypoglycaemia (the Hypo COMPaSS trial). BMC Endocrine Disorders. 2012; 12:33.	No relevant outcomes and does not match review question (study protocol for the HypoCOMPaSS trial)
MACLEOD 1994 MacLeod KM, Deary IJ, Graham KS, Hepburn DA, Frier BM. Hypoglycaemia unawareness in adult patients with Type I diabetes: Relationship to severe hypoglycaemia and cognitive impairment. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 1994; 7(4):205-212.	No relevant outcomes and does not match review question (incidence of severe hypoglycaemia in patients with hypoglycaemia unawareness, no intervention).
MANSELL 2012 Mansell P, Grant L, Cooke D, Rea R, Taylor C, Speight J et al. Diabetes self-management strategies after DAFNE structured education. Diabetic Medicine. 2012; 29:8-9.	Conference abstract. Population does not match protocol
MARAN 1993 Maran A, Lomas J, Archibald H, Macdonald IA, Gale EA, Amiel SA. Double blind clinical and laboratory study of hypoglycaemia with human and porcine insulin in diabetic patients reporting hypoglycaemia unawareness after transferring to human insulin. BMJ. 1993; 306(6871):167-171.	Intervention and comparator do not match protocol (human and porcine insulin – insulins not relevant to current practice)
MATEJKO 2013 Matejko B, Grzanka M, Kiec-Wilk B, Malecki MT, Klupa T. Clinical factors affecting the perception of hypoglycemia in type 1 diabetes patients treated with personal insulin pumps. Annals of Agricultural and Environmental Medicine. 2013; 20(1):152-154.	No relevant outcomes and does not match review question (correlation between hypoglycaemia perception and severe hypoglycaemia in CSII patients, no intervention).
MCBRIDE 2013 McBride M, Eggleston AS, Jones T, Ly T. Health-related quality of life in patients with type 1 diabetes and impaired hypoglycaemia awareness: The role of sensor-augmented insulin pump therapy with automated insulin suspension. Value in Health. 2013; 16(7):A448.	Conference abstract.

Reference	Reason for exclusion
MCCALL 2012 McCall AL. Insulin therapy and hypoglycemia. Endocrinology and Metabolism Clinics of North America. 2012; 41(1):57-87.	Review article
MIURA 2012 Miura J, Kajiura M, Hoshina S, Kobayashi H, Uchigata Y. The investigation of risk factor for the hypoglycemia unawareness in patients with type 1 diabetes using CGMS. Diabetes. 2012; 61:A554.	Conference abstract. Population does not match protocol
MOHEET 2012 Moheet A, Kumar A, Chow L, Eberly LE, Seaquist ER. History of severe hypoglycemia and score on clarke questionnaire is associated with blunted counterregulatory response to experimental hypoglycemia in patients with type 1 diabetes. Diabetes. 2012; 61:A99.	No relevant outcomes and does not match review question (correlation between Clarke score and symptoms in patients with IAH, no intervention).
MULHAUSER 1998 Muhlhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors of severe hypoglycaemia in adult patients with Type I diabetes--a prospective population based study. Diabetologia. 1998; 41(11):1274-1282.	No relevant outcomes and does not match review question (risk factors for severe hypoglycaemia in patients with type 1 diabetes).
PEDERSEN 2001 Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. Lancet. 2001; 357(9264):1248-1253.	No relevant outcomes and does not match review question (ACE genotype and risk of severe hypoglycaemia).
PEDERSEN 2003 Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2003; 19(3):232-240.	No relevant outcomes and does not match review question (correlation between severe hypoglycaemia and hypoglycaemia unawareness)
PEDERSEN 2009A Pedersen-Bjergaard U. Severe hypoglycaemia in type 1 diabetes: impact of the renin-angiotensin system and other risk factors. Danish Medical Bulletin. 2009; 56(4):193-207.	Review article
RADERMECKER 2010 Radermecker RP, Saint Remy A, Scheen AJ, Bringer J, Renard E. Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. Diabetes and Metabolism. 2010; 36(5):409-413.	Population does not match protocol (patients with >6 BG values <60mg/dl in the past 14 days, severe hypoglycaemias requiring third party assistance not reported). Paper included in glucose monitoring review
RAY 2013 Ray T, Choudhary P, Mansell P, Heller S, Amiel SA, Hopkins D. Dose adjustment for normal eating (DAFNE) structured education reduces progression to continuous subcutaneous	Conference abstract

Reference	Reason for exclusion
insulin infusion (CSII) among patients being considered for insulin pump therapy at enrolment. Diabetic Medicine. 2013; 30:7-8.	
ROBERTSON 1999 Robertson RP. Prevention of recurrent hypoglycemia in type 1 diabetes by pancreas transplantation. Acta Diabetologica. 1999; 36(1-2):3-9.	Review article checked for references
RYAN 2004 Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes. 2004; 53(4):955-962.	No relevant outcomes – does not report IAH as an outcome
RYAN 2005 Ryan EA, Paty BW, Senior PA, Lakey JR, Bigam D, Shapiro AM. Beta-score: an assessment of beta-cell function after islet transplantation. Diabetes Care. 2005; 28(2):343-347.	No relevant outcomes – score of beta-cell function before and after islet transplantation
SCHOPMAN 2011 Schopman JE, Geddes J, Frier BM. Frequency of symptomatic and asymptomatic hypoglycaemia in Type 1 diabetes: effect of impaired awareness of hypoglycaemia. Diabetic Medicine. 2011; 28(3):352-355.	No relevant outcomes and does not match review question (incidence of severe hypoglycaemia in patients with hypoglycaemia unawareness, no intervention).
SEJLING 2012 Sejling A-S, Thorsteinsson B, Pedersen-Bjergaard U. The effect of mild and severe hypoglycaemia and hypoglycaemia awareness on 12-year all-cause mortality in type 1 diabetes. Diabetologia. 2012; 55:S98.	Conference abstract. No relevant outcomes and does not match review question (correlation study)
SHEILS 2012 Sheils E, Knott J, Cavan D, Shaban C. Fear of hypoglycaemia: Is there an association with glycaemic control, hypoglycaemic symptoms and diabetes emotional distress in people with Type 1 diabetes? Diabetic Medicine. 2012; 29:157.	Conference abstract. No relevant outcomes and does not match review question (correlation between hypoglycaemia fear score and hypoglycaemia unawareness)
SPEIGHT 2011 Speight J, Barendse S, Singh H, Amiel SA, Elliot J, Evans M et al. The Hypo Awareness Questionnaire: Design of a novel measure of awareness of hypoglycaemia for use in the UK Hypo COMPaSS trial. Diabetic Medicine . 2011; 28:181.	Conference abstract. No relevant outcomes and does not match review question (design of IAH scoring system)
STREJA 2005 Streja D. Can continuous glucose monitoring provide objective documentation of hypoglycemia unawareness? Endocrine Practice. 2005; 11(2):83-90.	No relevant outcomes and does not match review question (CMBG for detection of IAH)
TAHIR 2013 Tahir M, Patel NH. Quality of life scores, treatment	Conference abstract. Population does not match protocol

Reference	Reason for exclusion
satisfaction scores and hypoglycaemia awareness scores are more valid measures of the impact of continuous subcutaneous insulin infusion (CSII) initiation than HbA1c in patients with Type 1 diabetes. Diabetic Medicine. 2013; 30:199.	
TAN 2012A Tan HK, Flanagan DE. Impaired hypoglycaemia awareness in Type 1 diabetes in an outpatient setting. Diabetic Medicine. 2012; 29:130.	Conference abstract. No relevant outcomes and does not match review question (prevalence of IAH)
THOMAKOS 2010 Thomakos P, Teh MM, Samarasighe Y, Pernet A, Wilson B, Choudhary P et al. The effect of modafinil on counterregulatory and cognitive responses to experimental hypoglycaemia in type 1 diabetic patients with hypoglycaemia unawareness. Diabetologia. 2010; 53:S238.	Conference abstract. Intervention duration does not match protocol.
UNGER 2011 Unger J, Parkin C. Recognition, prevention, and proactive management of hypoglycemia in patients with type 1 diabetes mellitus. Postgraduate Medicine. 2011; 123(4):71-80.	Review article
UNGER 2012 Unger J. Uncovering undetected hypoglycemic events. Diabetes, Metabolic Syndrome and Obesity. 2012; 5:57-74.	Review article
VENEMAN 1994 Veneman TF, van Haeften TW. Hypoglycaemia unawareness in insulin-dependent diabetes mellitus. European Journal of Clinical Investigation. 1994; 24(12):785-793.	Review article

K.7 Ketone monitoring

K.7.1 Ketone self-monitoring and in-hospital monitoring

Reference	Reason for exclusion
FULOP 1999 M. Fulop, V. Murthy, A. Michilli, J. Nalamati, Q. Qian, and A. Saitowitz. Serum beta-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. Arch.Intern.Med. 159 (4):381-384, 1999.	Wrong intervention/comparison/outcomes: correlation between blood β-OHB and serum CO_2 and anion gap. Does not compare to urine B-OHB test. Doesn't give results to predict severity of DKA. Population is 70% type 1 diabetes and 30% type 2 diabetes.
MACKAY 2010 L. MacKay, M. J. Lyall, S. Delaney, J. A. McKnight, and M. W. J. Strachan. Are blood ketones a better predictor than urine ketones of acid base	Did not use the standard cut-off for ketone B-HBA measurement, and did not give comparison of

Reference	Reason for exclusion
balance in diabetic ketoacidosis? Pract.Diabetes Int. 27 (9):396-399, 2010.	the results for blood vs. urine measurements.
BULL 2007 SV. Bull, IS. Douglas, M Foster, and RK. Albert. Mandatory protocol for treating adult patients with diabetic ketoacidosis decreases intensive care unit and hospital lengths of stay: results of a nonrandomized trial. *Crit.Care Med.* 35 (1):41-46, 2007.	Wrong comparison: effects of a treatment protocol rather than monitoring.
MATTA 2004 M. P. Matta, V. Melki, S. Bessiere-Lacombe, and H. Hanaire-Broutin. What are capillary blood ketone levels in type 1 diabetic patients using CSII in normal conditions of insulin delivery? *Diabetes Metab.* 30 (6):543-547, 2004.	Wrong outcomes: does not link ketone measurements with clinical episodes
MESA 2006A J. Mesa, D. Salcedo, Hde L. Calle, E. Delgado, J. Novoa, F. Hawkins, G. S. Navarrete, M. Parramon, and D. Acosta. Detection of ketonemia and its relationship with hyperglycemia in type 1 diabetic patients. *Diabetes Res.Clin.Pract.* 72 (3):292-297, 2006.	Wrong outcomes: does not link ketone measurements with clinical episodes
PATEL 2011A N. P. Patel, S. Dronavalli, and I. Lat. Evaluation of a diabetic ketoacidosis protocol to improve quality and cost of care. Pharmacotherapy 31 (10):387e, 2011.	Conference abstract
MANIKANDAN 2012 R. M. Manikandan, J. Abel, R. Verdaguer, R. Rajendran, and M. G. Masding. Management of diabetic ketoacidosis improves with implementation of care pathway. Diabet.Med. 29:123, 2012.	Conference abstract
EL SAMAHY 2011 M. H. El Samahy, N. S. Elbarbary, H. H. El-Ashry, and D. A. Abdel-Hameed. Monitoring of blood beta-hydroxybutyrate as a screening test for diabetic ketoacidosis at the Emergency Department. Pediatr Diabetes 12:40, 2011.	Abstract not available
ESPIN 2010 B J. Espin, M L. Garcia, and D. Epstein. Economic evaluation of monitoring systems of ketones in blood for the diagnosis and prevention of ketoacidosis. Anonymous. Anonymous. Seville:Andalusian Agency for Health Technology Assessment (AETSA). 2010.	Not in English
TURAN 2008 S. Turan, A. Omar, and A. Bereket. Comparison of capillary blood ketone measurement by electrochemical method and urinary ketone in treatment of diabetic ketosis and ketoacidosis in children. Acta Diabetol. 45 (2):83-85, 2008.	Wrong population: children
KHAN 2004 A. S. Khan, J. A. Talbot, K. L. Tieszen, E. A. Gardener, J. M. Gibson, and J.	Wrong population: healthy volunteers

Reference	Reason for exclusion
P. New. Evaluation of a bedside blood ketone sensor: the effects of acidosis, hyperglycaemia and acetoacetate on sensor performance. Diabet.Med. 21 (7):782-785, 2004.	
FARRELL 2011 K. Farrell and D. J. Holmes-Walker. Mobile phone support is associated with reduced ketoacidosis in young adults. Diabet.Med. 28 (8):1001-1004, 2011.	Mixed population (type 1 diabetes and type 2 diabetes, % type 1 diabetes not given) and no type 1 diabetes subgroup analysis
HENDEY 1997 G. W. Hendey, T. Schwab, and T. Soliz. Urine ketone dip test as a screen for ketonemia in diabetic ketoacidosis and ketosis in the Emergency Department. Ann.Emerg.Med. 29 (6):735-738, 1997.	Wrong intervention/comparison: diagnosis of DKA (sensitivity and specificity of urine ketone dip test (not compare with blood test).
TIMMONS 1998 J. A. Timmons, P. Myer, A. Maturen, R. Webster, E. Schaller, J. Leikin, and R. Barkin. Use of beta-hydroxybutyric acid levels in the emergency department. Am.J.Ther. 5 (3):159-163, 1998.	Wrong comparisons: compares the levels of acetone rather than B-OHB. Both groups that are compared are B-OHB positive and there are no details for any B-OHB negative groups (which is what we want to compare).
WIJAYA 2004 I. P. Wijaya, P. Soewondo, D. Widodo, and A. W. Sudoyo. Beta-hydroxybutirate levels as a determinant for the success of diabetic ketoacidosis management. Acta Med Indones 36 (2):70-77, 2004.	Wrong outcomes: gives correlation with pH, pCO2 and HCO3 rather than to clinical outcomes.
NAUNHEIM 2006 R Naunheim, T J. Jang, G Banet, A Richmond, and J McGill. Point-of-care test identifies diabetic ketoacidosis at triage. Acad.Emerg.Med. 13 (6):683-685, 2006.	Wrong intervention /comparison: diagnosis of DKA (sensitivity and specificity of blood β-OHB (not compare with urine test). Population: ED pts with Bld Glc >250 mg/dl OR signs/symptoms of DKA.
SMITH 2008 S. W. Smith, A. F. Manini, T. Szekely, and R. S. Hoffman. Bedside detection of urine beta-hydroxybutyrate in diagnosing metabolic acidosis. Acad.Emerg.Med. 15 (8):751-756, 2008.	Wrong study type: *in vitro* study testing new composition of chemicals in urine dipstick test
GUERCI 2003 B. Guerci, M. Benichou, M. Floriot, P. Bohme, S. Fougnot, P. Franck, and P. Drouin. Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. Diabetes Care 26 (4):1137-1141, 2003.	Wrong comparison: plasma vs. capillary blood ketone measurement every hour for 5hrs after CSII stopped.
SEFENDINI 2008 E. Sefedini, M. Prasek, Z. Metelko, B. Novak, and Z. Pinter. Use of capillary beta-hydroxybutyrate for the diagnosis of diabetic ketoacidosis at emergency room: Our one-year experience. Diabetol.Croat. 37 (3):73-78, 2008.	Wrong outcomes/study: relationship between blood and urine ketones and DKA – only gives sensitivity and specificity for the urine ketone mesaurement and not the blood ketone

Reference	Reason for exclusion
	measurements.
PRISCO 2006 F. Prisco, A. Picardi, D. Iafusco, R. Lorini, L. Minicucci, M. E. Martinucci, S. Toni, F. Cerutti, I. Rabbone, R. Buzzetti, A. Crino, and P. Pozzilli. Blood ketone bodies in patients with recent-onset type 1 diabetes (a multicenter study). Pediatr Diabetes 7 (4):223-228, 2006.	Wrong population - children
ARORA 2011 Point-of-care beta-hydroxybutyrate testing for assessing diabetic ketoacidosis severity prior to treatment in the emergency department	Wrong outcomes: gives correlation with pH, anion gap and HCO3 (as measures of severity) rather than to clinical outcomes.
TABOULET 2004 P. Taboulet, L. Haas, R. Porcher, J. Manamani, J. P. Fontaine, J. P. Feugeas, and J. F. Gautier. Urinary acetoacetate or capillary beta-hydroxybutyrate for the diagnosis of ketoacidosis in the Emergency Department setting. *Eur.J.Emerg.Med.* 11 (5):251-258, 2004.	The Taboulet 2007 study (already included) also includes the same pt cohort as this, plus additional patients.
MACGILLIVRAY 1982 M. H. MacGillivray, P. K. Li, J. T. Lee, B. J. Mills, M. L. Voorhess, T. I. Putnam, and P. A. Schaefer. Elevated plasma beta-hydroxybutyrate concentrations without ketonuria in healthy insulin-dependent diabetic patients. *J.Clin.Endocrinol.Metab.* 54 (3):665-668, 1982.	Wrong follow-up time: 1 day of measurements in healthy type 1 diabetes pts (so not the in-hospital question; and imapprotpriate follow-up time for the self-monitoring question).
NIWA 1985 T. Niwa, K. Yamada, T. Ohki, and H. Furukawa. 3-Hydroxyhexanoid acid: An abnormal metabolite in urine and serum of diabetic ketoacidotic patients. *J.CHROMATOGR.BIOMED.APPL.* 337 (1):1-7, 1985.	Type of diabetes not mentioned.
WALLACE 2001 T. M. Wallace, N. M. Meston, S. G. Gardner, and D. R. Matthews. The hospital and home use of a 30-second hand-held blood ketone meter: guidelines for clinical practice. *Diabet.Med.* 18 (8):640-645, 2001.	Type of diabetes not mentioned.
FEDERICI 2006 M. O. Federici and M. M. Benedetti. Ketone bodies monitoring. *Diabetes Res.Clin.Pract.* 74 (SUPPL. 2):S77-S81, 2006.	SR- used as a source of references
CHASE 2004 H. P Chase. Detection of ketosis and monitoring of diabetic ketoacidosis. *Manag.Care* 13 (4 Suppl):5-6, 2004.	Short article about DKA; not a clinical study.
CHARLES 2007 R. A. Charles, Y. M. Bee, P. H. K. Eng, and S. Y. Goh. Point-of-care blood ketone testing: screening for diabetic ketoacidosis at the emergency department. *Singapore Med J* 48 (11):986-989, 2007.	Does not give outcome results for the type 1 diabetes pts – only shows the levels of ketones in pts with type 1 diabetes and not if linked to DKA.
CRANE 2004 ML. Crane. Role of blood ketone testing in sick-day management. *Manag.Care* 13 (4 Suppl):14-21, 2004.	Overview article about blood ketone testing; not a clinical study.

Reference	Reason for exclusion
FABIETTI 2006 P. G. Fabietti, V. Canonico, M. Orsini Federici, E. Sarti, and M. Massi Benedetti. Model based study on monitoring ketone bodies to improve safety in intensive insulin therapy. *Int J Artif Organs* 29 (6):596-601, 2006.	Does not answer our question: interruption of sc insulin and modellingthe rise in ketones.
FULOP 1999 M. Fulop, V. Murthy, A. Michilli, J. Nalamati, Q. Qian, and A. Saitowitz. Serum beta-hydroxybutyrate measurement in patients with uncontrolled diabetes mellitus. *Arch.Intern.Med.* 159 (4):381-384, 1999.	Already excluded from original review: Wrong intervention/comparison/outcomes: correlation between blood β-OHB and serum CO_2 and anion gap. Does not compare to urine B-OHB test. Doesn't give results to predict severity of DKA. Population is 70% type 1 diabetes and 30% type 2 diabetes.
GUERCI 2005 B. Guerci, N. Tubiana-Rufi, B. Bauduceau, R. Bresson, et al. Advantages to using capillary blood beta-hydroxybutyrate determination for the detection and treatment of diabetic ketosis. *Diabetes Metab.* 31 (4 Pt 1):401-406, 2005.	Review article/recommendations on hydroxybutyrate determination.
LAFFEL 2000 L. Laffel. Sick-day management in type 1 diabetes. *Endocrinol.Metab.Clin.North Am.* 29 (4):707-723, 2000.	Review article - used as a source of references
MCBRIDE 1991 M. McBride, A. S. Eggleston, T. Jones, and T. Ly. Health-related quality of life in patients with type 1 diabetes and impaired hypoglycaemia awareness: The role of sensor-augmented insulin pump therapy with automated insulin suspension. *Value Health* 16 (7):A448, 2013.	Case report. Does not answer the question: a new method for measurement and its description.
NIWA 1982 T. Niwa, K. Maeda, T. Ohki, and J. Sakakibara. Identification of 2-hydroxy-2-methyllevulinic acid in urine and serum of diabetic patients with ketoacidosis. *J Chromatogr* 228:59-65, 1982.	Type of diabetes not mentioned. Wrong ketone – not commonly tested for: 2-hydroxy-2-methyllevulinic acid
PLUDDEMANN 2011 A Pluddemann, Carl Heneghan, Christopher P. Price, Jane Wolstenholme, and Matthew Thompson. Point-of-care blood test for ketones in patients with diabetes: primary care diagnostic technology update. *Br J Gen Pract* 61 (589):530-531, 2011.	Overview of ketone testing; not a clinical study.
WESTERBERG 2013 DP. Westerberg. Diabetic ketoacidosis: evaluation and treatment. *Am Fam Physician* 87 (5):337-346, 2013.	Overview of DKA and its treatment; not a clinical study..
ARORA2012	Article currently unavailable.

Reference	Reason for exclusion
Arora S, Menchine M. The role of point-of-care beta-hydroxybutyrate testing in the diagnosis of diabetic ketoacidosis: a review. Hospital Practice. 2012; 40(2):73-78.	
PRISCO 2006 Prisco F, Picardi A, Iafusco D, Lorini R, Minicucci L, Martinucci ME et al. Blood ketone bodies in patients with recent-onset type 1 diabetes (a multicenter study). Pediatric Diabetes. 2006; 7(4):223-228	Already ordered for original review. Study was excluded as wrong population - children
KLOCKER 2013 Klocker AA, Phelan H, Twigg SM, Craig ME. Blood beta-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in Type 1 diabetes: a systematic review. Diabetic Medicine. 2013; 30(7):818-824	Already ordered for original review. Study was excluded as SR and thus used as source of references.
HARRIS 2005 Harris S, Ng R, Syed H, Hillson R. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabetic Medicine. 2005; 22(2):221-224	Already ordered for original review. Study was included.
SAMUELSSON 2002 U Samuelsson and Johnny Ludvigsson. When should determination of ketonemia be recommended? *Diabetes Technol.Ther.* 4 (5):645-650, 2002.	Wrong population: children and young people.
WIGGAM 1997 (ID 620) M. I. Wiggam, M. J. O'Kane, R. Harper, A. B. Atkinson, D. R. Hadden, E. R. Trimble, and P. M. Bell. Treatment of diabetic ketoacidosis using normalization of blood 3- hydroxybutyrate concentration as the endpoint of emergency management: A randomized controlled study. *Diabetes Care* 20 (9):1347-1352, 1997.	Wrong outcomes: does not report any of our pre-specified outcomes. Just levels of ketones.
SCHWAB 1999 T. M. Schwab, G. W. Hendey, and T. C. Soliz. Screening for ketonemia in patients with diabetes. *Ann Emerg Med* 34 (3):342-346, 1999.	Wrong population: mixture of diabetes and non-diabetics at the ED (only 27% with diabetes, and unknown if type 1 diabetes or not). All had hyperglycaemia.
BECK 2014 RW. Beck, D Raghinaru, R.P Wadwa, H. Peter Chase, DM. Maahs, BA. Buckingham, and In Home Closed Loop Study Group. Frequency of morning ketosis after overnight insulin suspension using an automated nocturnal predictive low glucose suspend system. *Diabetes Care* 37 (5):1224-1229, 2014.	Wrong intervention: ketone levels measured the morning after using a closed loop system that suspends insulin. Assesses the effect of the closed-loop system on ketones.
FIRESTONE 2013 R. Firestone, K. Pandya, P. Parker, and J. Duby. Effect of a conservative-correction DKA protocol on clinical outcomes in hospitalized patients. *Crit.Care Med.* 41 (12 SUPPL. 1):A16, 2013.	Conference abstract
HATHCOCK 2014 A. Hathcock, S. Ganji, I. Pathmanathan, H. Hedian, and A. Niyogi.	Conference abstract

Reference	Reason for exclusion
Monitoring DKA & HHS with urine dipstick: A sticky situation. *J.Gen.Intern.Med.* 29:S152, 2014.	
CHILDERS 2014 K. A. Childers, Perkins J. Caraway, G. Dogbey, and J. H. Shubrook. Health care provider adherence to guidelines in diagnosing diabetic ketoacidosis in the emergency department. *Diabetes* 63:A309, 2014.	Conference abstract
QIAO 2014 Y Qiao, Z Gao, Y Liu, Y Cheng, M Yu, L Zhao, Y Duan, and Y Liu. Breath ketone testing: a new biomarker for diagnosis and therapeutic monitoring of diabetic ketosis. *Biomed Res Int* 2014:869186, 2014.	Wromng outcomes – not those pre-specified in our protocol. Looks at correlations between breath, urine and blood ketones.
SMULOWITZ 2014 P. Smulowitz, T. Lee, M. Blackburn, M. Kennedy, O. Hamdy, R. Wolfe, and C. Tibbles. Reducing hospital length of stay for diabetic ketoacidosis using a novel ED observation pathway. *Acad.Emerg.Med.* 21 (5 SUPPL. 1):S293, 2014.	Conference abstract
KLOCKER 2013 A. A. Klocker, H. Phelan, S. M. Twigg, and M. E. Craig. Blood beta-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in Type 1 diabetes: a systematic review. *Diabet.Med.* Epublication, 2013.	SR used for references. No additional relevant references found to those we already have.
VANELI 2003 M. Vanelli, G. Chiari, C. Capuano, B. Iovane, A. Bernardini, and T. Giacalone. The direct measurement of 3-beta-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment. *Diabetes Nutr Metab* 16 (5-6):312-316, 2003.	Wrong population: children only (but compares blood vs. urine ketones)
SHEIKJ-ALI 2008 M. Sheikh-Ali, B. S. Karon, A. Basu, Y. C. Kudva, L. A. Muller, J. Xu, W. F. Schwenk, and J. M. Miles. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes Care* 31 (4):643-647, 2008.	Wrong comparison: Blood ketone measurement but does not compare with urine ketones.

K.8 Arterial risk control

K.8.1 Aspirin

Reference	Reason for exclusion
DELACRUZ 2010 J. P. De la Cruz, A. Guerrero, E. Rueda, J. Munoz-Marin, N. Jebrouni, and J. A. Gonzalez Correa. Efficacy and safety of sustained-release aspirin in patients with chronic coronary disease. *Eur.J.Clin.Pharmacol.* 66:S60, 2010.	Abstract not available
ANG 2010 X. Ang, R. Dignan, M. Gonzalez, I. Shugman, D. Parikh, Y. Goh, S. Lo, D. Leung, P. Nguyen, R. Rajaratnam, A. Hopkins, C. Juergens, and J. French. Risk factor	Abstract not available

Reference	Reason for exclusion
outcomes and revascularisation choice in diabetic patients considered for coronary revascularisation. *Heart Lung Circul.* 19:S61, 2010.	
BELCH 2008 J. Belch, A. MacCuish, I. Campbell, S. Cobbe, R. Taylor, R. Prescott, R. Lee, J. Bancroft, S. MacEwan, et al. Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group, and Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 337:a1840, 2008.	POPADAD trial – wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis.
BARTOLUCCI 2011 Alfred A. Bartolucci, Michal Tendera, and George Howard. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am.J.Cardiol.* 107 (12):1796-1801, 2011.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes, type 2 diabetes, CV disease or healthy people, with no type 1 diabetes subgroup analysis.
RAJU 2009 N. C. Raju, M. Sobieraj-Teague, and J. W. Eikelboom. A meta-analysis of randomized controlled trials of aspirin in primary prevention of cardiovascular disease. *Blood* 114 (22), 2009.	Abstract of meta-analysis - wrong population: trials used are mixed type 1 diabetes, type 2 diabetes, CV disease or healthy people, with no type 1 diabetes subgroup analysis.
DEBERARDIS 2009 G De Berardis, M Sacco, GFM. Strippoli, F Pellegrini, G Graziano, G Tognoni, and A Nicolucci. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 339:b4531, 2009.	Conference abstract of meta-analysis – wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis.
LI 2009 L. Li. Aspirin in the primary prevention of vascular disease: Meta-analysis from randomised trials. *Cardiology* 114:141-142, 2009.	Abstract – wrong population: non-diabetic.
BUTALIA 2011A S Butalia, A A. Leung, WA. Ghali, and DM. Rabi. Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovascular diabetology* 10:25, 2011.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
CALVIN 2009A AD. Calvin, NR. Aggarwal, MH Murad, Q Shi, MB. Elamin, JB. Geske, M.M Fernandez-Balsells, FN. Albuquerque, JF. Lampropulos, et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Care* 32 (12):2300-2306, 2009.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes, type 2 diabetes, CV disease or healthy people, with no type 1 diabetes subgroup analysis.
CALLES 2010 J. Calles-Escandón, L. C. Lovato, D. G. Simons-Morton, D. M. Kendall, R. Pop-Busui, R. M. Cohen, D. E. Bonds, V. A. Fonseca, F. Ismail-Beigi, M. A. Banerji,	ACCORD trial – wrong population: type 2 diabetes

Reference	Reason for exclusion
A. Failor, and B. Hamilton. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 33 (4):721-727, 2010.	
MOEREMANS 2009A K. Moeremans, M. Lamotte, K. Wittrup-Jensen, and M. Pignone. The heath economic value of aspirin in the primary prevention of cardiovascular disease in diabetic patients. *Eur.Heart J.* 30:233, 2009.	Abstract – cost-effectiveness study: wrong population: mixed type 1 diabetes and type 2 diabetes with no type 1 diabetes subgroup analysis.
UENO 2011A H Ueno, H Koyama, Y Mima, S Fukumoto, S Tanaka, T Shoji, M Emoto, T Shoji, Y Nishizawa, and M Inaba. Comparison of the effect of cilostazol with aspirin on circulating endothelial progenitor cells and small-dense LDL cholesterol in diabetic patients with cerebral ischemia: a randomized controlled pilot trial. *J Atheroscler Thromb* 18 (10):883-890, 2011.	RCT – wrong population: mixed type 1 diabetes and type 2 diabetes with cerebral ischaemia, with no type 1 diabetes subgroup analysis. Wrong comparison intervention – cilostazol.
DAS 2010 J. R. Das, S. Eshaghian, G. A. Diamond, P. K. Shah, and S. Kaul. Aspirin therapy for primary versus secondary prevention of cardiovascular disease: An updated meta-analysis. *J.Am.Coll.Cardiol.* 55 (10 SUPPL 1):A140, 2010.	Conference abstract of meta-analysis - wrong population: trials used are mixed type 1 diabetes, type 2 diabetes, CV disease or healthy people, with no type 1 diabetes subgroup analysis.
DEBERADIS 2007 G De Berardis, M Sacco, V Evangelista, A Filippi, CB. Giorda, G Tognoni, U Valentini, A Nicolucci, and D. ACCEPT. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* 8:21, 2007.	ACCEPT-D study – trial protocol. Wrong population: mixed type 1 diabetes and type 2 diabetes, with no planned type 1 diabetes subgroup analysis.
ZHANG 2010 C. Zhang, A. Sun, P. Zhang, C. Wu, S. Zhang, M. Fu, K. Wang, Y. Zou, and J. Ge. Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Diabetes Res.Clin.Pract.* 87 (2):211-218, 2010.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
YOUNIS 2010 N Younis, S Williams, B Ammori, and H Soran. Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis. *Expert Opin Pharmacother* 11 (9):1459-1466, 2010.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
TERAMOTO 2010 T. Teramoto, K. Shimada, S. Uchiyama, M. Sugawara, Y. Goto, N. Yamada, S. Oikawa, K. Ando, N. Ishizuka, T. Yamazaki, K. Yokoyama, M. Murata, and Y. Ikeda. Rationale, design, and baseline data of the Japanese Primary Prevention Project (JPPP)-a randomized, open-label, controlled trial of aspirin versus no aspirin in patients with multiple risk factors for vascular events. *Am.Heart J.* 159 (3):361-369, 2010.	JPPP trial - –trial protocol. Wrong population: mixed type 1 diabetes and type 2 diabetes, with no planned type 1 diabetes subgroup analysis.

Reference	Reason for exclusion
STAVRAKIS 2011 S. Stavrakis, J. A. Stoner, M. Azar, S. Wayangankar, and U. Thadani. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Am.J.Med.Sci.* 341 (1):1-9, 2011.	Meta-analysis - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
WELIN 2009A L. Welin, L. Wilhelmsen, A. Bjornberg, and A. Oden. Aspirin increases mortality in diabetic patients without cardiovascular disease: A Swedish record linkage study. Pharmacoepidemiol Drug Saf 18 (12):1143-1149, 2009.	Not an RCT. Wrong population: mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
SOEJIMA 2010A H Soejima, T Morimoto, Y Saito, and H Ogawa. Aspirin for the primary prevention of cardiovascular events in patients with peripheral artery disease or diabetes mellitus. Analyses from the JPAD, POPADAD and AAA trials. Thromb.Haemost. 104 (6):1085-1088, 2010.	SR and no meta-analysis - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
FORT 2013 P. Fort, S. M. Waters, and F. Lifshitz. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: Bolus versus no bolus. *J.Pediatr.* 96 (1):36-40, 1980.	Conference abstract; wrong comparison: aspirin vs. aspirin/omeprazole combination. Wrong population: already had history of CV events, thus is not a primary prevention study.
OPOLSKY 2012 G. Opolski, K. Strojek, M. Kurzelewski, M. Ostrowski, and D. Rabczenko. Cardiovascular therapy, diagnostic procedures, and control of risk factors in patients with diabetes or coronary artery disease in Poland: the KardiaPol registry. *Pol Arch Med Wewn* 122 (9):413-421, 2012.	Wrong population: diabetes, but excluded type 1 diabetes.
DIETRICH 2014 E. Dietrich and K. Davis. A Statin a Day to Keep the Doctor Away? Comparing Aspirin and Statins for Primary Prevention of Cardiovascular Disease. *Ann.Pharmacother.* 48 (9):1238-1241, 2014.	Overview article – not diabetic population.
DILLINGER 2012A J. G. Dillinger, Sollier C. Bal dit, P. Henry, and L. Drouet. Aspirin efficacy in diabetes. *Diabetes Metab.* 38:S96, 2012.	Conference abstract
OKADA 2013 S Okada, T Morimoto, H Ogawa, M Sakuma, H Soejima, M Nakayama, S Sugiyama, H Jinnouchi, M Waki, N Doi, M Horii, H Kawata, et al. and investigators for the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial. Effect of low-dose aspirin on primary prevention of cardiovascular events in Japanese diabetic patients at high risk. *Circ J* 77 (12):3023-3028, 2013.	Type 2 diabetes
OKADA 2013A S. Okada, T. Morimoto, H. Ogawa, M. Sakuma, H. Soejima, M. Ohtorii, M. Nakayama, N. Doi, Y. Akai, H. Jinnouchi, M. Waki, S. Sugiyama, S. Uemura,	Conference abstract

Reference	Reason for exclusion
and Y. Saito. Long-term use of low-dose aspirin develops proteinuria in patients with diabetes: A reanalysis of jpad study. *Circulation* 128 (22 SUPPL. 1), 2013.	
PARK 2012 B. J. Park, Y. S. Park, N. K. Choi, Y. J. Lee, M. S. Kim, C. W. Lee, D. Y. Kang, S. Y. Park, J. E. Park, N. R. Lee et al. Aspirin prescription pattern among diabetic patients for prevention of cardiovascular disease. Anonymous. Anonymous. National Evidence-based Healthcare Collaborating Agency (NECA). 3, 2012.	Not in English
YUHARA 2014 H Yuhara, DA. Corley, F Nakahara, T Nakajima, J Koike, M Igarashi, T Suauki, and T Mine. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. *J Gastroenterol* 49 (6):992-1000, 2014.	SR – used as a source of references. None meet our review's inclusion criteria.
Additional studies from old GL and cross-referencing SRs, MAs and other GLs	
ID 1299 NHS Centre for Reviews and Dissemination. Aspirin for the secondary prophylaxis of vascular disease in primary care. Anonymous. Anonymous. University of Newcastle upon Tyne, Centre for Health Services Research; York: University of York, Centre for Health Economics. 1998. Old GL bibliography.	CRD brief overview of MAs on aspirin. Gives no type 1 diabetes subgroup data.
CAPRIE 1996A Anonymous. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 348 (9038):1329-1339, 1996.	CAPRIE study – wrong population: mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
BHATT 2002 D. L. Bhatt, S. P. Marso, A. T. Hirsch, P. A. Ringleb, W. Hacke, and E. J. Topol. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am.J.Cardiol. 90 (6):625-628, 2002.	CAPRIE study (additional analysis) – wrong population: mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
COLWELL 1997 J. A. Colwell. Aspirin therapy in diabetes. *Diabetes Care* 20 (11):1767-1771, 1997.	SR but no MA - wrong population: trials used are mixed type 1 diabetes and type 2 diabetes, with no type 1 diabetes subgroup analysis.
ATC 1994 (Antiplatelet Trialists' Collaboration) Anonymous. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ (Clinical research ed.)* 308 (6921):81-106, 1994.	ATC SR/MA - wrong population: trials used are mixed population not just diabetes; diabetes subgroup analysis but no specific type 1 diabetes subgroup analysis.
JONSSON 2003 B. Jönsson, L. Hansson, and N. O. Stålhammar. Health economics in the Hypertension Optimal Treatment (HOT) study: costs and cost-effectiveness of intensive blood pressure lowering and low-dose aspirin in patients with	HOT study - Health economic analysis. Wrong population: mixed type 1 diabetes and type 2

Reference	Reason for exclusion
hypertension. *J.Intern.Med.* 253 (4):472-480, 2003.	diabetes, with no type 1 diabetes subgroup analysis.
ECCLES 1998 M. Eccles, N. Freemantle, and J. Mason. North of England evidence based guideline development project: guideline on the use of aspirin as secondary prophylaxis for vascular disease in primary care. North of England Aspirin Guideline Development Group. BMJ (Clinical research ed.) 316 (7140):1303-1309, 1998.	Guidelines on aspirin use in vascular disease (North of England). Recommendations and evidence given for various subgroups including diabetes mellitus, however trials are not exclusively type 1 diabetes.

K.9 Inpatient management

K.9.1 IV insulin

Reference	Reason for exclusion
85 (SACKS 1979) Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. Annals of Internal Medicine. 1979; 90:36-42.	Unclear population – not sure if type 1 diabetes - just says DKA
943 (MALMBERG 1994) Malmberg KA, Efendic S, Ryden LE. Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. A report from the multicenter trial: DIGAMI. Diabetes Care. 1994; 17(9):1007-1014.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
ABELEV 2011 Abelev Z, Seth A, Patel R, Goldstein S, Bogun M, Paliou M et al. Continuous insulin infusion is associated with a reduced post-surgical length of stay, but not with the complication rate, in patients with diabetes mellitus undergoing coronary artery bypass graft. Journal of Endocrinological Investigation. 2011; 34(10):770-774.	Mixed population: type 1 diabetes and type 2 diabetes but % of type 1 diabetes not given, and no type 1 diabetes subgroup analysis.
ADAIR 2012 Adair R, Dreesman B, Subramanian A. Transition from intravenous to subcutaneous insulin is associated with worsening of glycemic control in critically ill patients-a retrospective cohort study. Critical Care Medicine. 2012; 40(12 SUPPL. 1):236.	Conference abstract. Wrong population – ICU patients excluding type 1 diabetes patients
ASSAAD 2010 Assaad-Khalil S, Fayed A, Aal AA. Insulin glargine in the early management of diabetic ketoacidosis; a randomized prospective pilot study. Critical Care Medicine. 2010; 38:A70.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
BAGG 1998 Bagg W, Sathu A, Streat S, Braatvedt GD. Diabetic ketoacidosis in adults at Auckland Hospital, 1988-1996.	Wrong outcomes: does not look at the effect of IV insulin.

Reference	Reason for exclusion
Australian and New Zealand Journal of Medicine. 1998; 28(5):604-608.	
BECKFORD 2011 Beckford R, Baram M. Continuous insulin infusion in treatment of diabetic ketoacidosis - How low can you go? American Journal of Respiratory and Critical Care Medicine. 2011; 183(1 MeetingAbstracts).	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
BEIK 2012 Beik N, Forni A, Anger K, Szumita P. Evaluation of a guideline for hyperglycemic emergencies at a tertiary academic medical center. Critical Care Medicine. 2012; 40(12 SUPPL. 1):71.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
BENDEZU 1978 Bendezu R, Wieland RG, Furst BH. Experience with low-dose insulin infusion in diabetic ketoacidosis and diabetic hyperosmolarity. Archives of Internal Medicine. 1978; 138(1):60-62.	Unclear population – not sure if type 1 diabetes - just says DKA
BOBERG 1976 Boberg J, Hedstrand H, Wide L. The early serum insulin response to intravenous glucose in patients with decreased glucose tolerance and in subjects with a familial history of diabetes mellitus. Scandinavian Journal of Clinical and Laboratory Investigation. 1976; 36(2):145-153.	Wrong setting: not in-hospital.
BONDUG 2013 Bondugulapati LNR, Phyu CHO, Irrinki L, Dixon A, Griffiths C. Audit on the management of diabetic ketoacidosis in a district general hospital. Diabetic Medicine. 2013; 30:80.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
BONNIER 2003 Bonnier M, Lonnroth P, Gudbjornsdottir S, Attvall S, Jansson PA. Validation of a glucose-insulin-potassium infusion algorithm in hospitalized diabetic patients. Journal of Internal Medicine. 2003; 253(2):189-193.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
BUTKIEWICZ 1995 Butkiewicz EK, Leibson CL, O'Brien PC, Palumbo PJ, Rizza RA. Insulin therapy for diabetic ketoacidosis. Bolus insulin injection versus continuous insulin infusion. Diabetes Care. 1995; 18(8):1187-1190.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
CARLOTTI 2013 Carlotti APdCP, St George-Hyslop C, Bohn D, Halperin ML. Hypokalemia during treatment of diabetic ketoacidosis: clinical evidence for an aldosterone-like action of insulin. Journal of Pediatrics. 2013; 163(1):207-212.	Wrong population: children and young people.

Reference	Reason for exclusion
CHASE 2007 Chase JG, Shaw GM, Lotz T, LeCompte A, Wong J, Lin J et al. Model-based insulin and nutrition administration for tight glycaemic control in critical care. Current Drug Delivery. 2007; 4(4):283-296.	Does not answer the question. Virtual modelling of a new protocol.
CHEE 2002 Chee F, Fernando T, van Heerden PV. Closed-loop control of blood glucose levels in critically ill patients. Anaesthesia and Intensive Care. 2002; 30(3):295-307.	Wrong population: critically ill, not type 1 diabetes.
DAVIS 1982 Davis TME, Holman RR, Eaton PM, Turner RC. A regular meal and insulin infusion regimen: Its use in the treatment of acute-onset ketotic diabetes and in stabilization of poorly controlled established diabetic subjects. Diabetes Care. 1982; 5(5):492-496.	Wrong population – poorly controlled patients but only inpatients as part of the study (recruited from outpatient clinics).
DROP 1977 Drop SL, Duval-Arnould JM, Gober AE, Hersh JH, McEnery PT, Knowles HC. Low-dose intravenous insulin infusion versus subcutaneous insulin injection: a controlled comparative study of diabetic ketoacidosis. Pediatrics. 1977; 59(5):733-738.	Wrong population: children and young people.
EDWARDS 1977 Edwards GA, Kohaut EC, Wehring B, Hill LL. Effectiveness of low-dose continuous intravenous insulin infusion in diabetic ketoacidosis. A prospective comparative study. Journal of Pediatrics. 1977; 91(5):701-705.	Wrong population: children. Unclear population – not sure if type 1 diabetes - just says DKA
ERSOZ 2006 Ersoz HO, Ukinc K, Kose M, Erem C, Gunduz A, Hacihasanoglu AB et al. Subcutaneous lispro and intravenous regular insulin treatments are equally effective and safe for the treatment of mild and moderate diabetic ketoacidosis in adult patients. International Journal of Clinical Practice. 2006; 60(4):429-433.	Unclear population – not sure if type 1 diabetes - just says DKA. Wrong setting: not in-hospital.
FISHER 1977 Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. New England Journal of Medicine. 1977; 297(5):238-241.	Unclear population – not sure if type 1 diabetes - just says DKA
FORT 1980 Fort P, Waters SM, Lifshitz F. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: Bolus versus no bolus. Journal of Pediatrics. 1980; 96(1):36-40.	Wrong population: children.
FURNARY 1999 (1649) Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous	Wrong population: ~36 % type 1 diabetes, and no type 1 diabetes subgroup analysis.

Reference	Reason for exclusion
intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Annals of Thoracic Surgery. 1999; 67(2):352-360.	
FURNARY 2006 Furnary AP. Rationale for glycemic control in cardiac surgical patients: The portland diabetic project. Insulin. 2006; 1(SUPPL. 1):S24-S29.	Wrong population: ~33 % type 1 diabetes, and no type 1 diabetes subgroup analysis.
FUSCO 2011 Fusco N, Yeung SY, Gonzales J. Evaluation of the treatment of diabetic ketoacidosis in the medical intensive care unit. Critical Care Medicine. 2011; 39:230.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
GAN 2009 Gan RM, Wong V, Cheung NW, McLean M. Effect of insulin infusion on electrocardiographic findings following acute myocardial infarction: importance of glycaemic control. Diabetic Medicine. 2009; 26(2):174-176.	Wrong population: AMI pts with diabetes or hyperglycaemia. |Unclear % which are type 1 diabetes, and no type 1 diabetes subgroup analysis.
GONZALEZ 1979 Gonzalez-Villalpando C, Blachley JD, Vaughan GM, Smith JD. Low- and high-dose intravenous insulin therapy for diabetic ketoacidosis. JAMA. 1979; 241(9):925-927.	Unclear population – not sure if type 1 diabetes - just says DKA
GONZALEZ 2002 Gonzalez-Michaca L, Ahumada M, Ponce-de-Leon S. Insulin subcutaneous application vs. continuous infusion for postoperative blood glucose control in patients with non-insulin-dependent diabetes mellitus. Archives of Medical Research. 2002; 33(1):48-52.	Wrong population: type 2 diabetes.
GOLIGHTLY 2006 Golightly LK, Jones MA, Hamamura DH, Stolpman NM, McDermott MT. Management of diabetes mellitus in hospitalized patients: Efficiency and effectiveness of sliding-scale insulin therapy. Pharmacotherapy. 2006; 26(10):1421-1432.	Wrong population: mixed diabetes and others; very few type 1 diabetes and no type 1 diabetes subgroup analysis.
GOYAL 2010 Goyal N, Miller JB, Sankey SS, Mossallam U. Utility of initial bolus insulin in the treatment of diabetic ketoacidosis. Journal of Emergency Medicine. 2010; 38(4):422-427.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
GRIMBERG 1999 Grimberg A, Cerri RW, Satin-Smith M, Cohen P. The "two bag system" for variable intravenous dextrose and fluid administration: benefits in diabetic ketoacidosis management. Journal of Pediatrics. 1999; 134(3):376-378.	Wrong population: children.

Reference	Reason for exclusion
GULAN 1987 Gulan M, Perlman K, Albisser AM, Pyper J, Zinman B. Controlled crossover study of subcutaneous and intravenous insulin infusion in type I diabetes. Diabetes Care. 1987; 10(4):453-460.	Wrong population – only inpatient as part of study. Comparison of IV and SC insulin during inpatient and outpatient periods. Both periods or outpatient alone data analysed
GUSTAFSON 2002 Gustafson PA, Zarro DL, Palanzo DA, Manley NJ, Montesano RM, Quinn M et al. Conventional approach to glucose management for diabetic patients undergoing coronary artery bypass surgery. Perfusion. 2002; 17(2):141-144.	Wrong population: mixed diabetes; % type 1 diabetes not given and no type 1 diabetes subgroup analysis. Wrong treatment: not just IV vs. SC insulin, but diferent solutions given as well (dextrose vs. saline).
HANNAN 1976 Hannan TJ, Stathers GM. Constant low dose insulin infusion in severe diabetes mellitus. Medical Journal of Australia. 1976; 1(1-2):11-13.	Unclear population – not sure if type 1 diabetes - just says diabetes and no type 1 diabetes subgroup analysis.
HEBER 1977 Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis. Prospective comparison with "conventional" insulin therapy. Archives of Internal Medicine. 1977; 137(10):1377-1380.	Unclear population – not sure if type 1 diabetes - just says DKA
HSIA 2012 Hsia E, Seggelke S, Gibbs J, Hawkins RM, Cohlmia E, Rasouli N et al. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. Journal of Clinical Endocrinology and Metabolism. 2012; 97(9):3132-3137.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
HUSBAND 1984 Husband DJ, Marshall SM, Walford S, Hanning I, Wright PD, Alberti KG. Continuous intraperitoneal insulin infusion in the management of severely brittle diabetes--a metabolic and clinical comparison with intravenous infusion. Diabetic Medicine. 1984; 1(2):99-104.	Wrong population: brittle diabetes; % type 1 diabetes not mentioned and no type 1 diabetes subgroup analysis.
HUSBAND 1985 Husband DJ, Alberti KGMM, Julian DG. Methods for the control of diabetes after acute myocardial infarction. Diabetes Care. 1985; 8(3):261-267.	Wrong population: mixed diabetes; % type 1 diabetes not given and no type 1 diabetes subgroup analysis.
IGNACZAK 2009 Ignaczak A, Saryusz-Wolska M, Szymanska-Garbacz E, Loba M, Czupryniak L. Risk factors for hypoglycaemia in patients with diabetes during continuous intravenous insulin infusion in hospital setting. Diabetologia. 2009; 52(S1):S400.	Conference abstract
IONESCU 1977 Ionescu-Tirgoviste C, Mincu I. Our experience in the insulin treatment of diabetic ketoacidosis. Revue Roumaine De	Unclear population – not sure if type 1 diabetes - just says DKA

Reference	Reason for exclusion
Medecine - Serie Medecine Interne. 1977; 15(3):281-287.	
JAHAGIRDAR 2007 Jahagirdar RR, Khadilkar VV, Khadilkar AV, Lalwani SK. Management of diabetic ketoacidosis in PICU. Indian Journal of Pediatrics. 2007; 74(6):551-554.	Wrong population: children.
JERVIS 2013 Jervis A, Champion S, Figg G, Langley J, Adams GG. Prevalence of diabetes ketoacidosis rises and still no strict treatment adherence. Current Diabetes Reviews. 2013; 9(1):54-61.	Unclear population – not sure if type 1 diabetes - just says DKA
JOHNSON 2007 Johnson SB, Baughcum AE, Hood K, Rafkin-Mervis LE, Schatz DA, Study Group. Participant and parent experiences in the parenteral insulin arm of the diabetes prevention trial for type 1 diabetes. Diabetes Care. 2007; 30(9):2193-2198.	Wrong population: children.
JOHNSTON 1997 Johnston JH, Cook AT. Treatment of diabetic ketoacidosis with small doses of insulin. Journal of the Royal Army Medical Corps. 1977; 123(1):32-36.	Wrong intervention: sc insulin (and no comparison)
KAROLI 2011 Karoli R, Fatima J, Salman T, Sandhu S, Shankar R. Managing diabetic ketoacidosis in non-intensive care unit setting: Role of insulin analogs. Indian Journal of Pharmacology. 2011; 43(4):398-401.	Wrong population: mixed diabetes DKA; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
KAUFMAN 1975 Kaufman IA, Keller MA, Nyhan WL. Diabetic ketosis and acidosis: the continuous infusion of low doses of insulin. Journal of Pediatrics. 1975; 87(5):846-848.	Wrong population: children.
KINSLEY 2009 Kinsley J, Jacob S. While we wait for the future: intensive glycemic management using combinations of subcutaneous and intravenous insulin in the critically ill. Critical Care Medicine. 2009; 37(12 SUPPL.):A325.	Conference abstract. Wrong intervention and comparison: hospital intense treatment protocol (combination of sc and IV insulin).
KITABCHI 1975 Kitabchi AE, Ayyagari V, Guerra S. Efficacy of low dose vs high dose insulin therapy in diabetic ketoacidosis (DKA). Diabetes. 1975; 24(sup 2):No-13.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
KITABCHI 1976 Kitabchi AE, Ayyagari V, Guerra SM. The efficacy of low-dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Annals of Internal Medicine. 1976; 84(6):633-638.	Unclear population – not sure if type 1 diabetes - just says DKA

Reference	Reason for exclusion
KITABCHI 2008 Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? Diabetes Care. 2008; 31(11):2081-2085.	Unclear population – not sure if type 1 diabetes - just says DKA
KRENTZ 1989 Krentz AJ, Hale PJ, Singh BM, Nattrass M. The effect of glucose and insulin infusion on the fall of ketone bodies during treatment of diabetic ketoacidosis. Diabetic Medicine. 1989; 6(1):31-36.	Unclear population – not sure if type 1 diabetes - just says DKA
LI 2006 Li JY, Sun S, Wu SJ. Continuous insulin infusion improves postoperative glucose control in patients with diabetes mellitus undergoing coronary artery bypass surgery. Texas Heart Institute Journal. 2006; 33(4):445-451.	Unclear population – not sure if type 1 diabetes - just says diabetes. Only 8% using insulin thus suggests population is mainly type 2 diabetes.
LUTTERMAN 1978 Lutterman JA, Adriaansen AAJ, Van 'T LA. Treatment of severe diabetic ketoacidosis. A comparison of two methods. Diabetologia. 1978; 15(3):no.	Unclear population – not sure if type 1 diabetes - just says DKA
MANIKANDAN 2012 Manikandan RM, Abel J, Verdaguer R, Rajendran R, Masding MG. Management of diabetic ketoacidosis improves with implementation of care pathway. Diabetic Medicine. 2012; 29:123.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
MAZER 2009 Mazer M, Chen E. Is subcutaneous administration of rapid-acting insulin as effective as intravenous insulin for treating diabetic ketoacidosis? Annals of Emergency Medicine. 2009; 53(2):259-263.	Unclear population – not sure if type 1 diabetes - just says DKA
MCKENNA 2000A McKenna K, Smith D, Tormey W, Thompson CJ. Acute hyperglycaemia causes elevation in plasma atrial natriuretic peptide concentrations in Type 1 diabetes mellitus. Diabetic Medicine. 2000; 17(7):512-517.	Wrong setting: not in-hospital; clamp study.
MCMULLIN 2007 McMullin J, Brozek J, McDonald E, Clarke F, Jaeschke R, Heels-Ansdell D et al. Lowering of glucose in critical care: a randomized pilot trial. Journal of Critical Care. 2007; 22(2):112-119.	Wrong population: critical care pts, not diabetes or type 1 diabetes.
MIROUZE 1980 Mirouze J, Selam JL, Pham TC, Chenon D. Programming of an open-loop system for i.v. insulin infusion in insulin-	Wrong setting: not in-hospital; closed and open loop infusion 'artificial pancreas'

Reference	Reason for exclusion
dependent diabetes. Acta Diabetologica Latina. 1980; 17(2):103-109.	
OLENG 2012 Oleng N, Gershengorn H. Management of DKA. Critical Care Medicine. 2012; 40(12 SUPPL. 1):73-74.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
OYIBO 2012 Oyibo SO, Sagi SV, Home C. Glycaemic control during enteral tube feeding in patients with diabetes who have had a stroke: A twice-daily insulin regimen. Practical Diabetes. 2012; 29(4):135-139.	Wrong population: mixed diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
PAOLISSO 1987 Paolisso G, Sgambato S, Passariello N, Scheen A, D'Onofrio F, Lefebvre PJ. Greater efficacy of pulsatile insulin in type I diabetics critically depends on plasma glucagon levels. Diabetes. 1987; 36(5):566-570.	Wrong setting: not in-hospital.
PAOLISSO 1988 Paolisso G, Sgambato S, Torella R, Varricchio M, Scheen A, D'Onofrio F et al. Pulsatile insulin delivery is more efficient than continuous infusion in modulating islet cell function in normal subjects and patients with type 1 diabetes. Journal of Clinical Endocrinology and Metabolism. 1988; 66(6):1220-1226.	Wrong setting: not in-hospital.
PAOLISSO 1990 Paolisso G, Sgambato S, Giunta R, Varricchio M, D'Onofrio F. Pulsatile rather than continuous glucagon infusion leads to greater metabolic derangements in insulin-dependent diabetic subjects. Diabete and Metabolisme. 1990; 16(1):42-47.	Wrong setting: not in-hospital.
PATEL 2011A Patel NP, Dronavalli S, Lat I. Evaluation of a diabetic ketoacidosis protocol to improve quality and cost of care. Pharmacotherapy. 2011; 31(10):387e.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
PINGET 1998 Pinget M, Jeandidier N. Long term safety and efficacy of intraperitoneal insulin infusion by means of implantable pumps. Hormone and Metabolic Research. 1998; 30(8):475-486.	Pumps not IV insulin.
PITERS 1975 Piters K, Goodman J, Bessman A. Treatment of diabetic ketoacidosis with continuous low dose intravenous insulin. Diabetes. 1975; 24(sup 2):No-14.	Conference abstract. Unclear population – not sure if type 1 diabetes - just says DKA
POIRIER 2004	Wrong population: children.

Reference	Reason for exclusion
Poirier MP, Greer D, Satin-Smith M. A prospective study of the "two-bag system'' in diabetic ketoacidosis management. Clinical Pediatrics. 2004; 43(9):809-813.	
QUIBRERA 1976 Quibrera R, Nava M, de Leon ED, Vidales M. Treatment of diabetes ketoacidosis, hyperosmolar coma and severe diabetes with low I.V. Intermitent doses of insulin. Revista De Investigacion Clinica; Organo Del Hospital De Enfermedades De La Nutricion. 1976; 28(1):1-6.	Wrong population: mixed diabetes; % type 1 diabetes not mentioned and no type 1 diabetes subgroup analysis.
RAGUSO 1994 Raguso CA, Mingrone G, Greco AV, Tataranni PA, De Gaetano A, Castagneto M. Dicarboxylic acids and glucose utilization in humans: effect of sebacate. Journal of Parenteral and Enteral Nutrition. 1994; 18(1):9-13.	Wrong intervention – not insulin: sebacate vs. saline
SELAM 1983 Selam JL, Slingeneyer A, Hedon B, Mares P, Beraud JJ, Mirouze J. Long-term ambulatory peritoneal insulin infusion of brittle diabetes with portable pumps: comparison with intravenous and subcutaneous routes. Diabetes Care. 1983; 6(2):105-111.	Wrong setting: not in-hospital.
SELAM 1985 Selam JL, Medlej R, M'Bemba J, Chevalier A, Guyon F, Ashworth L et al. Symptoms, hormones, and glucose fluxes during a gradual hypoglycaemia induced by intraperitoneal vs venous insulin infusion in Type I diabetes. Diabetic Medicine. 1995; 12(12):1102-1109.	Wrong setting: not in-hospital; clamp study.
SHAHSHAHANI 1977 Shahshahani MN, Guerrra SO, Kitabchi AE. Comparison of the absorption of insulin by intramuscular (IM) subcutaneous (SC) and intravenous (IV) routes in obese and lean non ketotic diabetic patients. Clinical Research. 1977; 25(1):58A.	Conference abstract. Full paper excluded from this review
SHAHSHAHANI 1978 Shahshahani MN, Kitabchi AE. Glucose-lowering effect of insulin by different routes in obese and lean nonketotic diabetic patients. J Clin Endocrinol Metab. 1978 Jul;47(1):34-40.	Wrong population: not inpatients; diabetic patients not previously received insulin treatment
SHOMALI 2011 Shomali ME, Herr DL, Hill PC, Pehlivanova M, Sharretts JM, Magee MF. Conversion from intravenous insulin to subcutaneous insulin after cardiovascular surgery: transition to target study. Diabetes Technology and Therapeutics. 2011; 13(2):121-126.	Wrong comparison: all groups given sc insulin.
SIMMONS 1994 (993)	Wrong population – 60% treated with insulin

Reference	Reason for exclusion
Simmons D, Morton K, Laughton SJ, Scott DJ. A comparison of two intravenous insulin regimens among surgical patients with insulin-dependent diabetes mellitus. Diabetes Educator. 1994; 20(5):422-427.	alone but does not specify type 1 diabetes (there is subgroup analysis for this group for the outcome '% patients in target range'.
SOLER 1975 Soler NG, FitzGerald MG, Wright AD, Malins JM. Comparative study of different insulin regimens in management of diabetic ketoacidosis. Lancet. 1975; 2(7947):1221-1224.	Unclear population – not sure if type 1 diabetes - just says severe DKA
STEFANIS 2003 Stefanidis A, Melidonis A, Tournis S, Zairis M, Handanis S, Beldekos D et al. Effect of intravenous insulin administration on left ventricular performance during non-ST-elevation acute coronary events in patients with diabetes mellitus. American Journal of Cardiology. 2003; 91(10):1237-1240.	Wrong population: type 2 diabetes.
STORK 2006 Stork ADM, Erkelens DW, Veneman TF. A practical insulin infusion algorithm for the establishment of euglycaemia in both lean and obese patients with type 1 and type 2 diabetes. Diabetes Research and Clinical Practice. 2006; 72(3):251-257.	Wrong setting: not in-hospital; clamp study.
SYDOR 2004 Sydor AR, Houlden RL. Inpatient care of patients with diabetes undergoing coronary artery bypass graft surgery in a Canadian tertiary-care hospital. Canadian Journal of Diabetes. 2004; 28(3):201-209.	Wrong population: mixed diabetes; % type 1 diabetes not mentioned and no type 1 diabetes subgroup analysis.
THOMAS 1977 Thomas DJB, Platt HS, Smythe P. Assessment of continuous insulin infusion for the management of insulin dependent diabetics, during and after surgery. Diabetologia. 1977; 13(4):No-317.	Conference abstract
THOMAS 1984 Thomas DJ, Platt HS, Alberti KG. Insulin-dependent diabetes during the peri-operative period. An assessment of continuous glucose-insulin-potassium infusion, and traditional treatment. Anaesthesia. 1984; 39(7):629-637.	No relevant outcomes reported
UDWADIA 2012 Udwadia F, Bhattacharyya A, Seshiah V, Kumar SB, Kumar S, Kumar SP et al. Intravenous insulin aspart in a hospital setting: Results from an observational study examining patient outcomes and physician preferences. Diabetes Management. 2012; 2(2):103-110.	Wrong population: mixed diabetes and non-diabetes; most diabetics are type 2 diabetes. No type 1 diabetes subgroup analysis.

Reference	Reason for exclusion
UMPIERREZ 2004 Umpierrez GE, Latif K, Stoever J, Cuervo R, Park L, Freire AX et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. American Journal of Medicine. 2004; 117(5):291-296.	Unclear population – not sure if type 1 diabetes - just says DKA. Authors contacted and informed us that the population was >70% type 1 diabetes. However, this study was agreed by the GDG to be excluded because it is DKA patients, and management of DKA is outside of the guideline scope.
UMPIERREZ 2004A Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care. 2004; 27(8):1873-1878.	Wrong population: mixed diabetes; % type 1 diabetes not mentioned and no type 1 diabetes subgroup analysis. Authors contacted and informed us that the population was >70% type 1 diabetes. However, this study was agreed by the GDG to be excluded because it is DKA patients, and management of DKA is outside of the guideline scope.
UMPIERREZ 2009 Umpierrez GE, Jones S, Smiley D, Mulligan P, Keyler T, Temponi A et al. Insulin analogs versus human insulin in the treatment of patients with diabetic ketoacidosis: a randomized controlled trial. Diabetes Care. 2009; 32(7):1164-1169.	Unclear population – not sure if type 1 diabetes - just says DKA. Authors contacted and informed us that the population was >70% type 1 diabetes. However, this study was agreed by the GDG to be excluded because it is DKA patients, and management of DKA is outside of the guideline scope.
VINCENT 2013 Vincent M, Nobecourt E. Treatment of diabetic ketoacidosis with subcutaneous insulin lispro: A review of the current evidence from clinical studies. Diabetes and Metabolism. 2013; 39(4):299-305.	Unclear population – not sure if type 1 diabetes - just says DKA. Wrong population: children.
WALTS 1981 Walts LF, Miller J, Davidson MB, Brown J. Perioperative management of diabetes mellitus. Anesthesiology. 1981; 55(2):104-109.	Wrong population: mixed diabetes; % type 1 diabetes not mentioned and no type 1 diabetes subgroup analysis.
WEINRAUCH 2010 Weinrauch LA, Sun J, Gleason RE, Boden GH, Creech RH, Dailey G et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. Metabolism: Clinical and Experimental. 2010; 59(10):1429-1434.	Wrong setting: not in-hospital; 12 months treatment.
HUI 2012 M. L. Hui, A. Kumar, and G. G. Adams. Protocol-directed insulin infusion sliding scales improve perioperative hyperglycaemia in critical care. *Perioperative Med.* 1 (1), 2012.	Review: used as source of references. References not relevant – as looked at by the chair. Most are mixed population and not type 1 diabetes.
MARVIN 2013 MR. Marvin, Silvio E. Inzucchi, and Brian J. Besterman. Computerization of the Yale insulin infusion protocol and potential insights into causes of hypoglycemia with intravenous insulin. *Diabetes Technol.Ther.* 15 (3):246-252,	Does not specify if type 1 diabetes or type 2 diabetes pts. Just says 'pts admitted to ICU who were treated with insulin infusion' Contacted authors and they were not able to provide this information.

Reference	Reason for exclusion
2013.	Assessment of a specific new technology – a computerised insulin dosing calculator.
HARA 2013 Jayme S. Hara, Aryan J. Rahbar, Meghan N. Jeffres, and Kenneth E. Izuora. Impact of a hyperglycemic crises protocol. *Endocr Pract* 19 (6):953-962, 2013.	Mixed population of type 1 diabetes and type 2 diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
CORNEY 2012 S. M. Corney, T. Dukatz, S. Rosenblatt, B. Harrison, R. Murray, A. Sakharova, and M. Balasubramaniam. Comparison of insulin pump therapy (continuous subcutaneous insulin infusion) to alternative methods for perioperative glycemic management in patients with planned postoperative admissions. *J Diabetes Sci Technol* 6 (5):1003-1015, 2012.	Already found study in pre-rerun evidene. Has been included in the review.
HSIA 2012 E. Hsia, S. Seggelke, J. Gibbs, R. M. Hawkins, E. Cohlmia, N. Rasouli, C. Wang, I. Kam, and B. Draznin. Subcutaneous administration of glargine to diabetic patients receiving insulin infusion prevents rebound hyperglycemia. *Journal of clinical endocrinology and metabolism* 97 (9):3132-3137, 2012.	Already found study in pre-rerun evidene. Has been excluded from the review due to being the wrong population: mixed diabetes.
VINCENT 2013 M. Vincent and E. Nobecourt. Treatment of diabetic ketoacidosis with subcutaneous insulin lispro: a review of the current evidence from clinical studies. *Diabetes Metab* 39 (4):299-305, 2013.	Already found study in pre-rerun evidene. Has been excluded from the review due to being the wrong population: children, and also DKA, not specifically type 1 diabetes.

K.10 Complications

K.10.1 Gastroparesis

Reference	Reason for exclusion
ABIDI 2006 N. Abidi, W. L. Starkebaum, and T. L. Abell. An energy algorithm improves symptoms in some patients with Gastroparesis and treated with gastric electrical stimulation. *Neurogastroenterol.Motil.* 18 (4):334-338, 2006.	Mixed population of diabetes and other conditions. No diabetes subgroup analysis done..
ABRAHAMSSON 2012 H. Abrahamsson. Treatment of Gastroparesis, nausea and vomiting - The role of gastric pacing. *Scand.J.Gastroenterol.* 47:S25, 2012.	Abstract. Not RCT. Not specific to type 1 diabetes
ANAPARTHY 2009 R Anaparthy, N Pehlivanov, J Grady, H Yimei, and P J. Pasricha. Gastroparesis and Gastroparesis-like syndrome: response to therapy and its predictors. Dig.Dis.Sci. 54 (5):1003-1010, 2009.	Retrospective study.
ANDERSSON 2010 S. Andersson, A. Elfvin, G. Ringstrom, H. Lonroth, H. Abrahamsson, and M.	Mixed population of diabetes and other

Reference	Reason for exclusion
Simren. A slow caloric satiety drinking test in patients with temporary and permanent gastric electrical stimulation. *Eur.J.Gastroenterol.Hepatol.* 22 (8):926-932, 2010.	conditions. No diabetes subgroup analysis done.
ANDERSSON 2010A S. Andersson, G. Ringstrom, A. Elfvin, M. Simren, H. Lonroth, and H. Abrahamsson. Temporary percutaneous gastric electrical stimulation: A novel technique tested in patients with non-established indications for gastric electrical stimulation. *Digestion* 83 (1-2):3-12, 2010.	Mixed population of diabetes and other conditions. No diabetes subgroup analysis done.
BELL 2002 R A. Bell, K Jones-Vessey, and JH. Summerson. Hospitalizations and outcomes for diabetic Gastroparesis in North Carolina. South.Med.J. 95 (11):1297-1299, 2002.	Does not look at treatment for gastroparesis.
BHARUCHA 2011 A. E. Bharucha, P. A. Low, M. Camilleri, D. D. Burton, Y. C. Kudva, P. Shah, and A. R. Zinsmeister. A prospective, randomized, placebo-controlled double-blind, dose-escalation trial of pyridostigmine for diabetes mellitus and constipation. *Gastroenterology* 140 (5 SUPPL. 1):S2-S3, 2011.	Abstract. Wrong population – diabetes and constipation not Gastroparesis
BRAATEN 1991 M. C Champion and J Braaten. Domperidone compared to cisapride in the management of gastroparesis. *Am.J.Gastroenterol.* 86:1309, 1991.	Conference abstract. Wrong comparison: cisapride vs. domperidone.
BRILEY 2011 Lauren Carney Briley, Steven P. Harrell, Allison Woosley, Jennifer Eversmann, and John M. Wo. National survey of physicians' perception of the cause, complications, and management of Gastroparesis. South.Med.J. 104 (6):412-417, 2011.	Physicians' opinions but not all about diabetic Gastroparesis, and no type 1 diabetes specific opinions.
BRODY 2008 Fred Brody, Khashayar Vaziri, Antoinette Saddler, Aamir Ali, Elizabeth Drenon, Brook Hanna, Esma Akin, Florencia Gonzalez, and Edy Soffer. Gastric electrical stimulation for Gastroparesis. J.Am.Coll.Surg. 207 (4):533-538, 2008.	Mixed population of diabetes and other conditions. No diabetes subgroup analysis done.
CAMILLERI 2008 M Camilleri, V Andresen, J Keller, P Layer, and V M. Montori. Pharmacological and non-pharmacological interventions for symptomatic Gastroparesis. *Cochrane Database of Systematic Reviews* Issue 2:CD007116, 2008.	Protocol of SR/MA – plan to do type 1 diabetes subgroup analysis. Actual full review not been published.
CHAMPION 1987 M. C Champion, K Gulenchyn, and T O'Leary. Domperidone improves symptoms and solid phase gastric emptying in diabetic gastroparesis. *Am J Gastroenterol* 82 (975), 1987.	Conference abstract – very old! Not enough detail for including data in review. Cant find a full publication.
CHU 2011 H. Chu, Z. Lin, L. Zhong, R. Mccallum, and X. Hou. A meta-analysis: The treatment of high-frequency gastric electrical stimulation for different kinds of Gastroparesis. *Gastroenterology* 140 (5 SUPPL. 1):S559-S560, 2011.	Abstract. Wrong population – mixed diabetic, idiopathic and surgical Gastroparesis.). % type 1 diabetes not given and no type 1 diabetes subgroup analysis.

Reference	Reason for exclusion
CHU 2012 H. Chu, Z. Lin, L. Zhong, R. W. Mccallum, and X. Hou. Treatment of high-frequency gastric electrical stimulation for Gastroparesis. *J.Gastroenterol.Hepatol.* 27 (6):1017-1026, 2012.	Systematic review and meta-analysis. No type 1 diabetes subgroup analysis. Used as a source of references.
DARAM 2010 S. Daram, C. J. Lahr, D. C. Spree, A. Kedar, and T. L. Abell. Gastric electrical response to different stimulation parameters via intraoperative Egg recordings. Gastroenterology 138 (5 SUPPL. 1):S315, 2010.	Mixed population - 28% diabetic. % type 1 diabetes not given and no type 1 diabetes subgroup analysis.
DARAM 2010A S. Daram, C. Lahr, D. Spree, A. Kedar, and T. Abell. Modulating energy settings to derive optimal EGG parameters in Gastroparesis. Neurogastroenterol.Motil. 22:72, 2010.	Mixed population - 29% diabetic. % type 1 diabetes not given and no type 1 diabetes subgroup analysis.
DESAUTELS 1995 (OLD GL REF 1946) S. G. Desautels, W. R. Hutson, P. E. Christian, J. G Moore, and F. L. Datz. Gastric emptying response to variable oral erythromycin dosing in diabetic gastroparesis. *Digestive Diseases & Sciences.* 40 (1):141-146, 1995.	Only gives results after 3 hours treatment. Wrong outcomes: not those pre-specified in our protocol.
DICKERSON 2010 R. N. Dickerson. Glucagon-like peptide-1: A kinder, gentler method to achieving glycemic control for critically ill patients? *Crit.Care Med.* 38 (5):1379-1380, 2010.	Comment/letter
DUMITRASCU 2000 D. L. Dumitrascu and M. Weinbeck. Domperidone versus metoclopramide in the treatment of diabetic gastroparesis. *Am.J.Gastroenterol.* 95 (1):316-317, 2000.	Only gives results after 1 day treatment – exact time not given. Letter to editor so not much detail provided.
DUPRE 2005 J. Dupre. Glycaemic effects of incretins in Type 1 diabetes mellitus: A concise review, with emphasis on studies in humans. *Regul.Pept.* 128 (2):149-157, 2005.	Review
EJSKJAER 2009 N. Ejskjaer, E. T. Vestergaard, P. M. Hellstrom, L. C. Gormsen, S. Madsbad, J. L. Madsen, T. A. Jensen, J. C. Pezzullo, J. S. Christiansen, L. Shaughnessy, and G. Kosutic. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic Gastroparesis. *Aliment.Pharmacol.Ther.* 29 (11):1179-1187, 2009.	Abstract
EJSKJAER 2010 N. Ejskjaer, G. Dimcevski, J. Wo, P. M. Hellstrom, L. C. Gormsen, I. Sarosiek, E. Softeland, T. Nowak, J. C. Pezzullo, L. Shaughnessy, G. Kosutic, and R. Mccallum. Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic Gastroparesis: A randomized, placebo-controlled study. *Neurogastroenterol.Motil.* 22 (10):1069, 2010.	Abstract
EJSKJAER 2011 N. Ejskjaer, J. Fleischer, J. Froekjaer, A. Drewes, P. F. Jensen, and P. Rask.	Abstract but withdrawn. Type 1 diabetes patients

Reference	Reason for exclusion
Severe symptoms of diabetic gastroparesis and overall frequency of hospital admissions is significantly relieved by gastric neurostimulation. *Diabetes* 60:A568, 2011.	treatment of Gastroparesis with neurostimulation. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
EJSKJAER 2012 N. Ejskjaer, R. Malik, L. Tarnow, P. Hellstrom, G. Dimcevski, J. C. Pezullo, R. Venuti, L. Shaughnessy, P. Charlton, G. Kosutic, and R. Mccallum. TZP-102 ghrelin receptor agonist improves symptoms of diabetic Gastroparesis in both type 1 and type 2 diabetes. *Diabetes* 61:A242, 2012.	Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
FRANZESE 2002 A. Franzese, O. Borrelli, G. Corrado, P. Rea, Nardo G. Di, A. L. Grandinetti, L. Dito, and S. Cucchiara. Domperidone is more effective than cisapride in children with diabetic gastroparesis. *Aliment.Pharmacol.Ther.* 16 (5):951-957, 2002.	Wrong population: children. Wrong comparison: cisapride.
FUTAGAMI 2009 S. Futagami, K. Iwakiri, T. Shindo, T. Kawagoe, A. Horie, M. Shimpuku, K. Gudis, K. Miyake, T. Tsukui, and C. Sakamoto. 5ht4-Agonist (Mosapride) improves the clinical symptoms in PPI-resistant NERD patients via improvement of gastric emptying. *Gastroenterology* 136 (5 SUPPL. 1):A529-A530, 2009.	Abstract. Wrong population – NERD not Gastroparesis
GLINKINA 2012 I. V. Glinkina, I. Y. Budennaia, A. V. Zilov, V. M. Makhov, and G. A. Melnichenko. Randomized, prospective, open-label, comparative study to evaluate the efficacy of itopride hydrochloride in the management of delayed gastric emptying in type 1 diabetic patients. *Diabetes* 61:A242, 2012.	Abstract
GUTIERREZ 2009 J. M. Gutierrez, K. Black, J. I. Allen, and E. M. Johnson. Reduced surgical revisions associated with placement of subpectoral gastric electrical stimulator: Six year experience at a single institution. *Gastroenterology* 136 (5 SUPPL. 1):A921, 2009.	Retrospective study.
HEER 1983 M. Heer, W. Muller-Duysing, I. Benes, M. Weitzel, M. Pirovino, J. Altorfer, and M. Schmid. Diabetic gastroparesis: treatment with domperidone--a double-blind, placebo-controlled trial. *Digestion* 27 (4):214-217, 1983.	Wrong outcomes.
HEJAZI 2011 R. A. Hejazi, I. Sarosiek, K. Roeser, and R. W. Mccallum. Does grading the severity of Gastroparesis based on scintigraphic gastric emptying predict the treatment outcome of patients with Gastroparesis? Dig.Dis.Sci. 56 (4):1147-1153, 2011.	Retrospective study. Used for information for the clinical introduction.
HELLSTROM 2011A P. M. Hellstrom, J. F. Tack, K. E. Stephens, M. E. Barton, L. S. Vasist, D. B. Richards, P. M. Williams, D. H. Alpers, and G. E. Dukes. A double-blind, randomized placebo-controlled phase II study of the pharmacodynamics,	Conference Abstract

Reference	Reason for exclusion
safety/tolerability, and pharmacokinetics of single doses of the motilin agonist GSK962040, in patients with type I diabetes mellitus (T1DM) and Gastroparesis. *Gastroenterology* 140 (5 SUPPL. 1):S813, 2011.	
HLEBOWICZ 2007 J. Hlebowicz, G. Darwiche, O. Bjorgell, and L.-O. Almer. Effect of apple cider vinegar on delayed gastric emptying in patients with type 1 diabetes mellitus: A pilot study. BMC Gastroenterol. 7, 2007.	Not specified intervention and not specified outcomes
HORIE 2009 Y. Horie, N. Hayashi, K. Dugi, and M. Takeuchi. Design, statistical analysis and sample size calculation of a phase IIb/III study of linagliptin versus voglibose and placebo. *Trials* 10:82, 2009.	Wrong treatment: linagliptin (not a Gastroparesis treatment)
JONES 2003 M. P. Jones and K. Maganti. A Systematic Review of Surgical Therapy for Gastroparesis. *Am.J.Gastroenterol.* 98 (10):2122-2129, 2003.	Systematic review with no meta-analysis. No type 1 diabetes subgroup analysis.
KIM 2006 Sung wan Kim, Il seon Shin, Jae min Kim, Ho cheol Kang, Ji ung Mun, Su jin Yang, and Jin sang Yoon. Mirtazapine for severe Gastroparesis unresponsive to conventional prokinetic treatment. *Psychosomatics* 47 (5):440-442, 2006.	Case report. N = 1 type 1 diabetes
KOCH 1995 K. L KOCH and S Bingaman. Withdrawal study of domperidone vs placebo in diabetic patients: effect on upper gasterointestinal symptoms and gastric myopelectrical activity. *Gastroenterology* 108 (A630), 1995.	Conference abstract. Only reports satiety outcome for the subgroup of diabetics with gastroparesis.
KOTHARI 2011 S. Kothari, T. H. Kothari, G. L. Montague, J. T. McNeese, D. C. Spree, C. J. Lahr, and T. L. Abell. Gastric electrical stimulation and sacral electrical stimulation: A long-term follow up study of dual device treatment. Gastroenterology 140 (5 SUPPL. 1):S610, 2011.	Mixed population - 22% diabetic. No diabetes subgroup analysis.
LATA 2003 P. F. Lata and D. L. Walbrandt Pigarelli. Chronic metoclopramide therapy for diabetic Gastroparesis. *Ann.Pharmacother.* 37 (1):122-126, 2003.	Systematic review with no meta-analysis. No type 1 diabetes subgroup analysis.
LEHMANN 1995A K Lehmann. Does combination prokinetic therapy benefit patients with refactory diabetic gasteroparesis. *Gastroenterology* 108 (A636), 1995.	Wrong comparison: cisapride vs. domperidone. Conference abstract.
LIN 2004 Zhiyue Lin, Jameson Forster, Irene Sarosiek, and Richard W. McCallum. Treatment of diabetic Gastroparesis by high-frequency gastric electrical stimulation. Diabetes Care 27 (5):1071-1076, 2004.	Retrospective study.
LIN 2006 Z. Lin, I. Sarosiek, J. Forster, and R. W. Mccallum. Symptom responses, long-term outcomes and adverse events beyond 3 years of high-frequency gastric electrical stimulation for Gastroparesis. Neurogastroenterol.Motil. 18 (1):18-	Retrospective study.

Reference	Reason for exclusion
27, 2006.	
MAGANTI 2003 K. Maganti, K. Onyemere, and M. P. Jones. Oral erythromycin and symptomatic relief of Gastroparesis: A systematic review. *Am.J.Gastroenterol.* 98 (2):259-263, 2003.	Systematic review with no meta-analysis. No diabetes subgroup analysis.
MASON 2005 Rodney J. Mason, John Lipham, Gordon Eckerling, Alan Schwartz, and Tom R. Demeester. Gastric electrical stimulation: an alternative surgical therapy for patients with Gastroparesis. *Arch.Surg.* 140 (9):841-848, 2005.	Retrospective case series (not prospective).
MILLER 1991 D Patterson and M Miller. Natural history of diabetic gastroparesis treated with cisparide or dompiderone. *Am.J.Gastroenterol.* 86 (1316):1316, 1991.	Wrong treatment: cisapride and domperidone; but results pooled together and no subgroup analysis for domperidone
MCCALLUM 2007 R. Mccallum, O. Cynshi, SJ. Gordon, MS. Kipnes, D. Einhorn, C. Clinkingbeard, MM. Schuster, G. Tougas, et al. Clinical trial: Effect of mitemcinal (a motilin agonist) on gastric emptying in patients with gastroparesis - A randomized, multicentre, placebo-controlled study. *Aliment.Pharmacol.Ther.* 26 (8):1121-1130, 2007.	Mitemcinal not used in UK
MCCALLUM 2007A R. W. Mccallum, O. Cynshi, T. Abell, R. Albery, K. Amin, C. Arauz-Pacheco, D. Arkin, G. August, et al. Efficacy of mitemcinal, a motilin agonist, on gastrointestinal symptoms in patients with symptoms suggesting diabetic gastropathy: A randomized, multi-center, placebo-controlled trial. *Aliment.Pharmacol.Ther.* 26 (1):107-116, 2007.	Mitemcinal not used in UK
MCCALLUM 2009 R. Mccallum, F. J. Brody, H. P. Parkman, J. M. Wo, T. V. Nowak, W. J. Snape, D. R. Lerew, L. Ruehlow, and I. Sarosiek. Enterra gastric electrical stimulation for diabetic gastroparesis: Results from a multicenter randomized study. *Gastroenterology* 136 (5 SUPPL. 1):A61-A62, 2009.	Not addressing specified interventions
MCCALLUM 2009A R. Mccallum, G. Dimcevski, J. Wo, P. M. Hellstrom, I. Sarosiek, E. Soofteland, J. Pezzullo, L. Shaughnessy, G. Kosutic, and N. Ejskjaer. Ghrelin agonist (TZP-101) and symptom relief in diabetic patients with Gastroparesis. Neurogastroenterol.Motil. 21:74, 2009.	Conference Abstract. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
MCCALLUM 2009A R. Mccallum, G. Dimcevski, J. Wo, P. M. Hellstrom, I. Sarosiek, E. Soofteland, J. Pezzullo, L. Shaughnessy, G. Kosutic, and N. Ejskjaer. Ghrelin agonist (TZP-101) and symptom relief in diabetic patients with Gastroparesis. *Neurogastroenterol.Motil.* 21:74, 2009.	Abstract. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
MCCALLUM 2010C R. Mccallum, N. Ejskjaer, P. Hellstrom, R. A. Malik, T. V. Nowak, J. C. Pezzullo,	Abstract. Wrong intervention: Ulimorelin

Reference	Reason for exclusion
L. Shaughnessy, G. Kosutic, and J. M. Wo. TZP-101, a potent ghrelin receptor agonist, is effective in diabetic patients with delayed gastric emptying and severe nausea/vomiting: Phase 2 subset study data. *Gastroenterology* 138 (5 SUPPL. 1):S64, 2010.	(TZP-101/2) – has been discontinued in the UK.
MCCALLUM 2011 R. Mccallum, J. M. Wo, R. P. Venuti, T. Esfandyari, M. M. Jamal, G. Dimcevski, L. Tarnow, R. A. Malik, P. M. Hellstrom, L. Shaughnessy, et al. TZP-102, ghrelin agonist phase 2 data: The improvement in symptoms of Gastroparesis (Nausea, early satiety, bloating and abdominal pain) significantly correlated with patient rating of overall treatment effect. *Gastroenterology* 140 (5 SUPPL. 1):S807, 2011.	Abstract. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
MCCALLUM 2011A Richard W. McCallum, Zhiyue Lin, Jameson Forster, Katherine Roeser, Qingjiang Hou, and Irene Sarosiek. Gastric electrical stimulation improves outcomes of patients with Gastroparesis for up to 10 years. Clinical Gastroenterology and Hepatology 9 (4):314, 2011.	Mixed population - 64% diabetic. % type 1 diabetes not given and no diabetes subgroup analysis.
MCKENNA 2008 Daniel McKenna, Gretchen Beverstein, Mark Reichelderfer, Eric Gaumnitz, and Jon Gould. Gastric electrical stimulation is an effective and safe treatment for medically refractory Gastroparesis. Surgery (USA) 144 (4):566-4, 2008.	Retrospective study.
MURRAY 2005 C. D. R. Murray, N. M. Martin, M. Patterson, S. A. Taylor, M. A. Ghatei, M. A. Kamm, C. Johnston, S. R. Bloom, and A. V. Emmanuel. Ghrelin enhances gastric emptying in diabetic Gastroparesis: A double blind, placebo controlled, crossover study. *Gut* 54 (12):1693-1698, 2005.	Looks at the wrong outcomes: not those specified in our protocol. Also is a clamp study, so only gives results after 180 mins.
MUSUNURU 2010 S Musunuru, G Beverstein, and J Gould. Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for Gastroparesis. World J.Surg. 34 (8):1853-1858, 2010.	Mixed population of diabetes and other conditions. No diabetes subgroup analysis done.
NAGLER 1981 J. Nagler and P. Miskovitz. Clinical evaluation of domperidone in the treatment of chronic postprandial idiopathic upper gastrointestinal distress. *Am.J.Gastroenterol.* 76 (6):495-499, 1981.	Wrong population: not diabetic.
OKAMOTO 2003 H. Okamoto, M. Nomura, Y. Nakaya, K. Uehara, K. Saito, M. Kimura, K. Chikamori, and S. Ito. Effects of epalrestat, an aldose reductase inhibitor, on diabetic neuropathy and Gastroparesis. *Intern.Med.* 42 (8):655-664, 2003.	Wrong population: type 2 diabetes
OLAUSSON E. A. Olausson, M. Alpsten, A. Larsson, H. Mattsson, H. Andersson, and S. Attvall. Small particle size of a solid meal increases gastric emptying and late postprandial glycaemic response in diabetic subjects with Gastroparesis. Diabetes Res.Clin.Pract. 80 (2):231-237, 2008.	Wrong population. Not specified outcome

Reference	Reason for exclusion
PATTERSON 1993 D Patterson. A multicenter placebo-controlled study of dompiderone in diabetic gastroparesis. *Gastroenterology* 104 (A564), 1993.	Conference abstract. Unable to imnd reference. Probably now published as PATTERSON 1999 and been included in this review.
RAMESHSHANKER2011 R. Rameshshanker, L. A. Smith, P. Southern, D. Whitelaw, and C. Beckett. Gastroparesis and botulinum toxin. *Gut* 60:A105-A106, 2011.	Conference abstract.
RASK 2010 P. Rask, P. F. Jensen, and N. Ejskjaer. Gastric neurostimulation significantly relieves symptoms of severe diabetic Gastroparesis and reduces frequency of hospital contacts. Diabetologia 53:S450-S451, 2010.	Abstract. Type 1 diabetes patients.
ROTUNDO 2011 A. Rotundo, A. Askari, F. Pata, C. B. Tang, M. Alexander-Williams, M. Harvey, and S. Kadirkamanathan. Factors affecting patient outcome, following surgical insertion of gastric electrical stimulator for Gastroparesis - 10 year experience in a single UK centre. Gastroenterology 140 (5 SUPPL. 1):S806-S807, 2011.	Mixed population - 24% diabetic. % type 1 diabetes not given and no type 1 diabetes subgroup analysis.
RUSSO 2004 A. Russo, J. E. Stevens, N. Giles, G. Krause, D. G. O'Donovan, M. Horowitz, and K. L. Jones. Effect of the motilin agonist KC 11458 on gastric emptying in diabetic Gastroparesis. *Aliment.Pharmacol.Ther.* 20 (3):333-338, 2004.	Early stage of drug trial – pre-licensing. Uses unknown drug 'KC-11458).
SAROSIEK 2009 I. Sarosiek, J. Forster, K. Roeser, J. Sarosiek, and R. Mccallum. The results of two-channel synchronized multipoint gastric electrical pacing effect on gastric emptying in patients with severe diabetic Gastroparesis. *Gastroenterology* 136 (5 SUPPL. 1):A780, 2009.	Abstract
SILVERS 1998A D. Silvers, M. Kipnes, V. Broadstone, D. Patterson, E. M. M. Quigley, R. Mccallum, N. K. Leidy, C. Farup, Y. Liu, and A. Joslyn. Domperidone in the management of symptoms of diabetic Gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clin.Ther. 20 (3):438-453, 1998.	DUPLICATE – already included this study (SILVERS 1998) in this review.
SINGH-FRANCO 2007 D. Singh-Franco, G. Robles, and D. Gazze. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin.Ther.* 29 (4):535-562, 2007.	Wrong treatment: pramlintide (not a Gastroparesis treatment)
SOLIMAN 2011 A. M. Soliman, A. Carlson, and M. R. Wittek. Impact of gastric electric stimulation on health state utilities of diabetic Gastroparesis patients: Results from a prospective clinical trial. *Value Health* 14 (3):A84, 2011.	Abstract
STERN 1989 W. R. Stern. Summary of the 34th meeting of the Food and Drug	Report of drugs advisory comitte. Not a clinical trial.

Reference	Reason for exclusion
Administration Gastrointestinal Drugs Advisory Committee. March 15 and 16, 1989 (omeprazole and domperidone). *Am.J.Gastroenterol.* 84 (11):1351-1355, 1989.	
STEVENS 2006 Julie E. Stevens, Antonietta Russo, Carol A. Delaney, Peter J. Collins, Michael Horowitz, and Karen L. Jones. Acute effects of C-peptide on gastric emptying in longstanding type 1 diabetes. *Clin.Auton.Res.* 16 (1):55-57, 2006.	Not addressing our specified outcomes
STEVENS 2008 J. E. Stevens, A. Russo, A. F. Maddox, C. K. Rayner, L. Phillips, N. J. Talley, M. Giguere, M. Horowitz, and K. L. Jones. Effect of itopride on gastric emptying in longstanding diabetes mellitus. Neurogastroenterol.Motil. 20 (5):456-463, 2008.	Itopride not available in the UK.
SUGUMAR 2008 A. Sugumar, A. Singh, and P. J. Pasricha. A systematic review of the efficacy of domperidone for the treatment of diabetic Gastroparesis. Clinical Gastroenterology and Hepatology 6 (7):726-733, 2008.	SR – used for refernces. Mixed population (type 1 diabetes and type 2 diabetes). % type 1 diabetes not given and no type 1 diabetes subgroup analysis.
TAKANASHI 2009 Hisanori Takanashi and Osamu Cynshi. Motilides: a long and winding road: lessons from mitemcinal (GM-611) on diabetic Gastroparesis. *Regul.Pept.* 155 (1-3):18-23, 2009.	Mitemcinal not used in the UK.
TOMOKANE 2004 Y. Tomokane, M. Nomura, S. Kujime, Y. Noda, N. Kondo, Y. Nakaya, and S. Ito. Clinical study on the effects of nizatidine on gastric motility and cardiac autonomic function: Investigations using electrogastrography and spectral analysis of heart rate variability. *Arzneim.-Forsch.Drug Res.* 54 (8):427-435, 2004.	Wrong population: type 2 diabetes
UENO 2010 N. Ueno, A. Inui, and Y. Satoh. The effect of mosapride citrate on constipation in patients with diabetes. *Diabetes Res.Clin.Pract.* 87 (1):27-32, 2010.	Wrong population: diabetics with constipation (not Gastroparesis)
VENKATESH 2008 V Venkatesh and K. P. Kulkarni. Itopride and pantoprazole outcomes in diabetic Gastroparesis trial (IPOD trial). *J.Indian Med.Assoc.* 106 (12):814-815, 2008.	Short report – little detail given.
VIJAYAKUMAR2005 V. Vijayakumar. Increased productivity and improved patient tolerance using the low fat meal radionuclide solid gastric emptying study. *J.Clin.Gastroenterol.* 39 (9):839, 2005.	Comment/letter
WANG 2004 L. Wang. Clinical observation on acupuncture treatment in 35 cases of	Wrong population: type 2 diabetes

Reference	Reason for exclusion
diabetic Gastroparesis. *J Tradit Chin Med* 24 (3):163-165, 2004.	
WANG 2008 C.-P. Wang, C.-H. Kao, W.-K. Chen, W.-Y. Lo, and C.-L. Hsieh. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of Gastroparesis. *J.Altern.Complement.Med.* 14 (7):833-839, 2008.	Wrong population: type 2 diabetes
WEI 2007 Y. Q. Wei and W. Y. Xie. Therapeutic effect of Weidong Kang on diabetic gastroparesis. *J.Clin.Rehab.Tissue Eng.Res.* 11 (34):6901-6904, 2007.	in Chinese
WO 2010 J. Wo, R. Malik, T. Nowak, W. Snape, P. M. Hellstrom, L. Shaughnessy, G. Kosutic, and R. Mccallum. TZP-101 (ghrelin agonist) effects on daily vomiting due to diabetic Gastroparesis (GP): Phase 2 subset analysis. *Neurogastroenterol.Motil.* 22:13-14, 2010.	Abstract
WO 2011 J. M. Wo, N. Ejskjaer, P. M. Hellstrom, R. A. Malik, J. C. Pezzullo, L. Shaughnessy, et al. Randomised clinical trial: Ghrelin agonist TZP-101 relieves Gastroparesis associated with severe nausea and vomiting - Randomised clinical study subset data. *Aliment.Pharmacol.Ther.* 33 (6):679-688, 2011.	Wrong intervention: Ulimorelin – has been discontinued in the UK
JANSSEN 2013 P Janssen, M. Scott Harris, Mike Jones, Tatsuhiro Masaoka, Ricard Farre, Hans Tornblom, Lukas Van Oudenhove, Magnus Simren, and Jan Tack. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am.J.Gastroenterol.* 108 (9):1382-1391, 2013.	SR – used as source of references. Have ordered 5 studies that seem relevant.
POTTER 2013 TG. Potter and KR. Snider. Azithromycin for the treatment of gastroparesis. *Ann.Pharmacother.* 47 (3):411-415, 2013.	SR – used as a source of references. None of the references meet our review inclusion criteria.
SHIN 2013B A Shin, M Camilleri, I Busciglio, D Burton, SA. Smith, A Vella, M Ryks, D Rhoten, and AR. Zinsmeister. The ghrelin agonist RM-131 accelerates gastric emptying of solids and reduces symptoms in patients with type 1 diabetes mellitus. *Clin.Gastroenterol.Hepatol.* 11 (11):1453-1459, 2013.	Early stage of drug trial – pre-licensing. Uses unknown drug 'RM 131).
WILLIAMS 2013 P. A. Williams, Y. Nikitina, A. Kedar, C. J. Lahr, T. S. Helling, and T. L. Abell. Long-Term Effects of Gastric Stimulation on Gastric Electrical Physiology. *J.Gastrointest.Surg.* 17 (1):50-56, 2013.	Wrong outcomes for the diabetic subgroup – not our pre-specified outcomes.
EJSKJAER 2013 N. Ejskjaer, J. M. Wo, T. Esfandyari, M. Mazen Jamal, G. Dimcevski, L. Tarnow, R. A. Malik, P. M. Hellstrom, E. Mondou, J. Quinn, F. Rousseau, and R. W. Mccallum. A phase 2a, randomized, double-blind 28-day study of TZP-102 a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol.Motil.*	Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.

Reference	Reason for exclusion
25 (2):e140-e150, 2013.	
CHEN 2012 J. Chen, I. Sarosiek, R. Mccallum, T. Abell, Y. Sun, N. Moody, and J. Yin. Chronic transcutaneous electroacupuncture ameliorates dyspeptic symptoms in patients with diabetic gastroparesis: A placebo-controlled multicenter clinical trial using a newly developed microstimulator. *Neurogastroenterol.Motil.* 24:170, 2012.	Conference abstract. Custom-made machine.
EJSKJAER 2012A N. Ejskjaer, R. Malik, L. Tarnow, P. Hellstrom, G. Dimcevski, J. Pezullo, L. Shaughnessy, R. Venuti, P. Charlton, G. Kosutic, and R. Mccallum. Severe symptomatic diabetic gastroparesis in type 1 and type 2 diabetes: Ghrelin receptor agonist treatment improves symptoms. *Diabetologia* 55:S25, 2012.	Conference abstract
EJSKJAER 2013A N. Ejskjaer, J. M. Wo, T. Esfandyari, Jamal M. Mazen, G. Dimcevski, L. Tarnow, R. Malik, P. M. Hellstrom, E. Mondou, J. Quinn, F. Rousseau, and R. W. Mccallum. Gastric emptying, glycemia, and upper gi symptoms are independent factors in diabetic gastroparesis. *Gastroenterology* 144 (5 SUPPL. 1):S739-S740, 2013.	Conference abstract. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
GILDEN 2013 J. L. Gilden, S. Paturi, S. Vysetti, B. G. Theckedath, J. Stoll, and R. Trotta. Effects of delayed gastric emptying on glucoregulation in patients with diabetes mellitus. *Clin.Auton.Res.* 23 (5):276, 2013.	Conference abstract. Not a treatment study. Wrong outcomes.
HASAN 2012 S. Hasan, C. J. Davis, J. C. Hammond, T. V. Nowak, L. Ruehr, and C. Ramsey. Gastric electrical stimulation for symptom control of patients with diabetic, idiopathic, and post surgical gastroparesis. *Gastroenterology* 142 (5 SUPPL. 1):S1084, 2012.	Conference abstract
KOCH 1989 K. L. Koch, R. M. Stern, W. R. Stewart, and M. W. Vasey. Gastric emptying and gastric myoelectrical activity in patients with diabetic gastroparesis: effect of long-term domperidone treatment. *Am.J.Gastroenterol.* 84 (9):1069-1075, 1989.	Wrong outcomes: myoelectrical activity.
LEE 2013A L. A. Lee, A. Unalp, E. Corless, K. P. Yates, H. P. Parkman, T. L. Abell, K. L. Koch, W. L. Hasler, P. J. Pasricha, W. J. Snape, L. T. Nguyen, R. W. Mccallum, I. Sarosiek, G. Farrugia, J. Tonascia, and F. A. Hamilton. Complementary and alternative medicine use in patients enrolled in gastroparesis registry. *Gastroenterology* 144 (5 SUPPL. 1):S740, 2013.	Conference abstract
MCCALLUM 2013 R. Mccallum, I. Sarosiek, T. Abell, Y. Sun, J. Chen, and J. Yin. Chronic transcutaneous electroacupuncture ameliorates dyspeptic symptoms in patients with diabetic gastroparesis. *J.Investig.Med.* 61 (2):463, 2013.	Conference abstract

Reference	Reason for exclusion
MCCALLUM 2013A R. W. Mccallum, E. Mondou, J. Quinn, C. Cosentino, and F. Rousseau. TZP-102-CL-G003 phase 2b study results: Oral TZP-102 once daily for 12 weeks in patients with diabetic gastroparesis. *Gastroenterology* 144 (5 SUPPL. 1):S160-S161, 2013.	Conference abstract. Wrong intervention: Ulimorelin (TZP-101/2) – has been discontinued in the UK.
MCCALLUM 2013 – metoclopramide R. W. Mccallum, W. G. Kramer, and M. R. Carlson. Pharmacokinetics of intranasal metoclopramide administration in patients with nausea, vomiting and gastroparesis. *Gastroenterology* 144 (5 SUPPL. 1):S730, 2013.	Conference abstract. Wrong outcomes – pharmacokinetics.
ORTIZ 2013 A. M. Ortiz, R. Pratiti, A. Alvarez, I. Sarosiek, and R. W. Mccallum. Clinical role and cardiovascular safety profile of chronic domperidone use. *Gastroenterology* 144 (5 SUPPL. 1):S738, 2013.	Conference abstract. Mixed population – diabetes and other; no diabetes subgroup analysis.
PARKMAN 2013A H. P. Parkman, M. R. Carlson, and D. Gonyer. Metoclopramide for diabetic gastroparesis: Comparison of a nasal spray formulation to conventional oral tablet administration. *Gastroenterology* 144 (5 SUPPL. 1):S729-S730, 2013.	Conference abstract> Nasal spray vs. oral tablets.
ROTUNDO 2012 A. Rotundo, S. S. Antonowicz, B. Lorenzi, P. Siriwardana, C. B. Tang, M. Harvey, and S. S. Kadirkamanathan. Long-term outcomes following surgical insertion of gastric electrical stimulator (GES) for refractory gastroparesis: A 5 year follow up. *Gastroenterology* 142 (5 SUPPL. 1):S844, 2012.	Conference abstract
SAROSIEK 2012 I. Sarosiek, R. Mccallum, T. Abell, Y. Sun, N. Moody, J. Chen, and J. Yin. Chronic electrical stimulation at acupuncture points improves dyspeptic symptoms in patients with diabetic gastroparesis. *Am.J.Gastroenterol.* 107:S57-S58, 2012.	Conference abstract
SAROSIEK 2013A I. Sarosiek, R. W. Mccallum, Y. Sun, D. Vasquez, T. L. Abell, J. Yin, and J. Chen. Self-administered needleless acupuncture therapy to control dyspepsia and gerd symptoms in patients diagnosed with diabetic gastroparesis. *Gastroenterology* 144 (5 SUPPL. 1):S135, 2013.	Conference abstract
SHIN 2013 A. Shin, M. Camilleri, I. A. Busciglio, D. D. Burton, S. A. Smith, A. Vella, M. Ryks, D. Rhoten, and A. R. Zinsmeister. Phase 1, randomized, placebo-controlled, single-dose, two-period, crossover study of RM-131 on pharmacodynamics and symptoms in type 1 diabetics with documented delayed gastric emptying. *Gastroenterology* 144 (5 SUPPL. 1):S738, 2013.	Conference abstract. Early stage of drug trial – pre-licensing. Uses unknown drug 'RM 131).
TIMRATANA 2012 P. Timratana, K. M. El-Hayek, H. Shimizu, M. Kroh, and B. Chand. Laparoscopic gastric pacer therapy for medical refractory diabetic and idiopathic gastroparesis. *Gastroenterology* 142 (5 SUPPL. 1):S1065, 2012.	Conference abstract

Reference	Reason for exclusion
WATTS 1985 G. F. Watts, M. Armitage, J. Sinclair, and R. D. Hill. Treatment of diabetic gastroparesis with oral domperidone. *Diabetic medicine : a journal of the British Diabetic Association* 2 (6):491-492, 1985.	Three case reports (N=1 each)
YANG 2013A M Yang, X Li, S Liu, Z Li, M Xue, D Gao, X Li, and S Yang. Meta-analysis of acupuncture for relieving non-organic dyspeptic symptoms suggestive of diabetic gastroparesis. *BMC Altern Med* 13 (1):311, 2013.	SR/MA. Used as source of references. All relevant refs were in Chinese or data taken from thesis.
BARTON 2014 M. E. Barton, T. Otiker, L. V. Johnson, D. C. Robertson, R. L. Dobbins, H. P. Parkman, P. M. Hellstrom, J. F. Tack, et al. A randomized, double-blind, placebo-controlled phase II study (MOT114479) to evaluate the safety and efficacy and dose response of 28 days of orally administered camicinal, a motilin receptor agonist, in diabetics with gastroparesis. *Gastroenterology* 146 (5 SUPPL. 1):S-20, 2014.	Conference abstract
CHEN 2012 L. Chen, X. F. Zhang, B. Q. Ku, X. C. Wang, C. Ma, J. Y. Liang, and J. Liu. [Effects of acupoint injection of autologous blood on symptoms and plasma motilin and gastrin levels of diabetic gastroparesis patients] [Chinese]. *Zhen ci yan jiu [Acupuncture research]* 37 (3):229-232, 246, 2012.	Article not in English.
CHONG 2014 B. Chong and B. Richmond. Gastric electrical stimulation for refractory gastroparesis: Defining predictors of response and redefining what constitutes a successful outcome. *Gastroenterology* 146 (5 SUPPL. 1):S-556, 2014.	Conference abstract
CHU 2012 H. Chu, Z. Lin, L. Zhong, R. W. McCallum, and X. Hou. Treatment of high-frequency gastric electrical stimulation for gastroparesis. *J.Gastroenterol.Hepatol.* 27 (6):1017-1026, 2012.	Already found study in pre-rerun literature. Was excluded due to being a SR/MA and used as ource of refernces.
MILLER 2014 ND Miller, Elad Schiff, Eran Ben-Arye, Joelle Singer, Tsachi Tsadok Perets, Shlomit Flaut, Nadav Sahar, Yaron Niv, and Ram Dickman. Benefits of acupuncture for diabetic gastroparesis: a comparative preliminary study. *Acupunct Med* 32 (2):139-145, 2014.	Wrong population: type 2 diabetes.
JABER 2012 S. A. Jaber, B. M. Fallatah, A.-A. Shehry, and M. Abdelmoeti. Comparison study of gastric emptying after performing sleeve gastrectomy with two diffierent techniques. *Surg.Endosc.Interv.Tech.* 26:S195, 2012.	Conference abstract
MALIK 2014 A. Malik and H. P. Parkman. Symptoms of nausea and postprandial fullness improve in gastroparetic patients receiving botulinum toxin a injection into the pylorus. *Gastroenterology* 146 (5 SUPPL. 1):S-612, 2014.	Conference abstract

Reference	Reason for exclusion
MEYER 2012 A. Meyer, P. Pallati, A. Shaligram, D. Oleynikov, and M. Goede. Partial longitudinal gastrectomy: A novel curative approach for gastroparesis. *Surg.Endosc.Interv.Tech.* 26:S313, 2012.	Conference abstract
PANG 2014 B. Pang, Q. Zhou, J.-L. Li, L.-H. Zhao, and X.-L. Tong. Treatment of refractory diabetic gastroparesis: Western medicine and traditional Chinese medicine therapies. *World J.Gastroenterol.* 20 (21):6504-6514, 2014.	SR – used as source of references.
PARKMAN 2014A H. P. Parkman, M. R. Carlson, and D. Gonyer. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. *Neurogastroenterol Motil* 26 (4):521-528, 2014.	Nasal spray, not oral administration.
PARKMAN 2014 H. P. Parkman, M. R. Carlson, and D. Gonyer. Metoclopramide nasal spray provides symptom relief in women with diabetic gastroparesis: Results of a phase 2B study. *Gastroenterology* 16 (5 SUPPL. 1):S-20, 2014.	Conference abstract
PASRICHA 2014 P. J. Pasricha, K. P. Yates, J. O. Clarke, A. Unalp, J. Tonascia, K. L. Koch, et al. Morbidity, mortality and predictors of improvement in patients with gastroparesis: 4-year outcomes from the gastroparesis clinical research consortium. *Gastroenterology* 146 (5 SUPPL. 1):S-136, 2014.	Conference abstract
SAAB 2014 I. Saab and K. McFarlin. Surgical outcomes after insertion of gastric neurostimulator for refractory gastroparesis: A single institution's experience. *Surg.Endosc.Interv.Tech.* 28:247, 2014.	Conference abstract
SAROSIEK 2014 I. Sarosiek, B. R. Davis, J. Forster, J. Liu, A. Dwivedi, and R. W. McCallum. Pyloroplasty combined with gastric electrical stimulation-is this the final solution for refractory gastroparesis? *Gastroenterology* 146 (5 SUPPL. 1):S616-S617, 2014.	Conference abstract
SAXENA 2014 P. Saxena, J. O. Clarke, I. Penas, A. A. Messallam, E. M. Stein, M. Nandwani, B. C. Roland, S. Dhalla, V. Kumbhari, et al. Refractory gastroparesis can be succesfully managed with transpyloric stent placement and fixation. *Gastroenterology* 146 (5 SUPPL. 1):S-771, 2014.	Conference abstract
TORNBLOM 2014 H. Tornblom, S. Kilincalp, G. Ringstrom, M. Simren, and H. Abrahamsson. One-year response rate to gastric electrical stimulation in patients selected for treatment by temporary percutaneous gastric electrical stimulation. *Gastroenterology* 146 (5 SUPPL. 1):S-612, 2014.	Conference abstract

K.10.2 Acute painful neuropathy

Reference	Reason for exclusion
ABBOTT 1998 Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care. 1998; 21(7):1071-1075.	Intervention and outcomes do not match protocol. Population does not match protocol – chronic diabetic neuropathy
ALI 2011 Ali N, Ali SH, Ahmed M, Javed A. Analysis of drug used for the treatment of complications of diabetes in a teaching hospital. Der Pharmacia Lettre. 2011; 3(4):163-177.	Incorrect study design (prevalence of complications)
ATLI 2005 Ali N, Ali SH, Ahmed M, Javed A. Analysis of drug used for the treatment of complications of diabetes in a teaching hospital. Der Pharmacia Lettre. 2011; 3(4):163-177.	Population does not match protocol - mixed population of type 1 diabetes (% not reported) and type 2 diabetes with no subgroup analysis. Painful diabetic neuropathy
BACKONJA 1998 Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998; 280(21):1831-1836.	Population does not match protocol - mixed population of type 1 diabetes (~25%) and type 2 diabetes with no subgroup analysis. Diabetic neuropathy.
BACKONJA 1999 Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. Epilepsia. 1999; 40 Suppl 6:S57-4.	Population does not match protocol - mixed population of type 1 diabetes (% not reported) and type 2 diabetes with no subgroup analysis. Diabetic neuropathy.
BATTLA 1981 Battla H, Silverblatt CW. Clinical trial of amitriptyline and fluphenazine in diabetic peripheral neuropathy. Southern Medical Journal. 1981; 74(4):417-418.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
BOGDANOV 2011 Bogdanov EI, Sakovets TG. [Efficiency of cerebrolysin in the diabetic polyneuropathy in patients with insulin-dependency diabetes mellitus]. Zhurnal Nevrologii i Psikhiatrii Imeni S S Korsakova/Ministerstvo Zdravookhraneniia i Meditsinsko? Promyshlennosti Rossi?Sko? Federatsii, Vserossi?Skoe Obshchestvo Nevrologov [i] Vserossi?Skoe Obshchestvo Psikhiatrov. 2011; 111(2):35-39.	Not in English
BOYLE 2012 Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 2012; 35(12):2451-2458.	Population does not match protocol - mixed population of type 1 diabetes (~13%) and type 2 diabetes with no subgroup analysis. Diabetic peripheral neuropathic pain.

Reference	Reason for exclusion
BRAVONBOER 1994 Bravenboer B, Hendrikse PH, Oey PL, van Huffelen AC, Groenhout C, Gispen WH et al. Randomized double-blind placebo-controlled trial to evaluate the effect of the ACTH4-9 analogue ORG 2766 in IDDM patients with neuropathy. Diabetologia. 1994; 37(4):408-413.	Intervention does not match protocol (neuropeptide hormone anologue). Population does not match protocol – established clinical neuropathy according to abnormal vibration or temperature thresholds
BURGI 1995 Bürgi U, Villiger L, Diem P. [Intensive insulin therapy--is it worth the effort?]. Therapeutische Umschau Revue Thérapeutique. 1995; 52(10):635-638.	Not in English
CALISSI 1995 Calissi PT, Jaber LA. Peripheral diabetic neuropathy: current concepts in treatment. Annals of Pharmacotherapy. 1995; 29(7-8):769-777.	Review article.
CALLAGHAN 2012 Callaghan BC, Little AA, Feldman EL, Hughes Richard AC. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database of Systematic Reviews. 2012; Issue 6:CD007543. DOI:10.1002/14651858.CD007543.pub2.	Intervention does not match protocol (MDIs or insulin pump). Population does not match protocol – distal symmetric polyneuropathy in type 1 diabetes and type 2 diabetes.
CAPSAISIN STUDY GROUP (ANON 1992) Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. Diabetes Care. 1992; 15(2):159-165.	Population does not match protocol - mixed population of type 1 diabetes (~50%) and type 2 diabetes with no subgroup analysis – painful peripheral polyneuropathy and/or radiculopathy.
CHADDA 1978 Chadda VS, Mathur MS. Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. Journal of the Association of Physicians of India. 1978; 26(5):403-406.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy (diabetes type not mentioned)
CHEW 1999 Chew EY. Disease management by prevention: The prospects for diabetic retinopathy. Disease Management and Health Outcomes. 1999; 6(5):279-290.	Review article
COHEN 1987 Cohen KL, Harris S. Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy. Archives of Internal Medicine. 1987; 147(8):1442-1444.	Population does not match protocol - mixed population of insulin-dependent (~65%) and non insulin-dependent with no subgroup analysis – symptomatic peripheral neuropathy.
CREPALDI 1983 Crepaldi G, Fedele D, Tiengo A, Battistin L, Negrin P, Pozza G et al. Ganglioside treatment in diabetic peripheral neuropathy: a multicenter trial. Acta Diabetologica Latina. 1983; 20(3):265-276.	Intervention does not match protocol (ganglioside). Population does not match protocol – peripheral neuropathy and electrophysiological impairment.

Reference	Reason for exclusion
DAVIS 1999 Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules. Diabetes Care. 1999; 22(11):1909-1910.	Incorrect study design (case-study), not full paper. Population does not match protocol – type 2 diabetes
DCCT (174) The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995; 44:968-983.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
DCCT (1930) The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. New England Journal of Medicine. 1993; 329(14):977-986.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
DCCT (ANON 1995E) Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney International. 1995; 47(6):1703-1720.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
DCCT (ANON 1995F) The effect of intensive diabetes therapy on the development and progression of neuropathy. Annals of Internal Medicine. 1995; 122(8):561-568.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
DCCT (ANON 1996C) The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes. 1996; 45(10):1289-1298.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
DEJGARD 1988 Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet. 1988; 1(8575-6):9-11.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
DUBY 2004 Duby JJ, Campbell RK, Setter SM, White JR, Rasmussen KA. Diabetic neuropathy: An intensive review. American Journal of Health-System Pharmacy. 2004; 61(2):160-176.	Review article
EISENBERG 2001 (1726) Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology. 2001; 57:505-509.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis- evidence of peripheral neuropathy for at least 6 months

Reference	Reason for exclusion
GIBBONS 2011 Gibbons CH, Freeman R. The prognosis and spectrum of disease in treatment induced diabetic neuropathy, a painful autonomic neuropathy. Clinical Autonomic Research. 2011; 21(4):280.	Conference abstract. Incorrect study design (case-series) and only reports the natural history, autonomic function and clinical neurophysiology in treatment-induced neuropathy (no intervention).
GIMBEL 2003 Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. Neurology. 2003; 60(6):927-934.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy (diabetes type not mentioned)
GOLDSTEIN 2005 Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005; 116(1-2):109-118.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – diabetic peripheral neuropathic pain
GOMEZ 1985 Gomez-Perez FJ, Rull JA, Dies H, Rodriquez-Rivera JG, Gonzalez-Barranco J, Lozano-Castaneda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. Pain. 1985; 23(4):395-400.	Population does not match protocol - mixed population of insulin-dependent (~20%) and non insulin-dependent with no subgroup analysis – painful diabetic polyneuropathy.
GOMEZ 1996 Gomez-Perez FJ, Choza R, Rios JM, Reza A, Huerta E, Aguilar CA et al. Nortriptyline-fluphenazine vs. carbamazepine in the symptomatic treatment of diabetic neuropathy. Archives of Medical Research. 1996; 27(4):525-529.	Population does not match protocol - mixed population of insulin-dependent (~40%) and non insulin-dependent with no subgroup analysis - diabetic polyneuropathy.
GOMEZ 2004 Gomez-Perez FJ, Perez-Monteverde A, Nascimento O, Aschner P, Tagle M, Fichtner K et al. Gabapentin for the treatment of painful diabetic neuropathy: Dosing to achieve optimal clinical response. British Journal of Diabetes and Vascular Disease. 2004; 4(3):173-178.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis - diabetic polyneuropathy.
GORSON 1999 (1730) Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. Journal of Neurology, Neurosurgery & Psychiatry. 1999; 66(2):251-252.	Population does not match protocol - mixed population of type 1 diabetes (% not reported) and type 2 diabetes with no subgroup analysis - diabetic polyneuropathy.
HALL 2010 Hall JA, Wang F, Myers Oakes TM, Utterback BG, Crucitti A, Acharya N. Safety and tolerability of duloxetine in the acute management of diabetic peripheral neuropathic pain: Analysis of pooled data from three placebo-controlled clinical trials. Expert Opinion on Drug Safety. 2010; 9(4):525-537.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis - diabetic peripheral neuropathy

Reference	Reason for exclusion
HARATI 1998 (1732) Harati Y, Gooch C, Swenson M, Edelman S, Greene D, Raskin P et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. Neurology. 1998; 50(6):1842-1846.	Population does not match protocol – type of diabetes not mentioned - diabetic peripheral neuropathy.
HARDY 2007 Hardy T, Sachson R, Shen S, Armbruster M, Boulton AJM. Does treatment with duloxetine for neuropathic pain impact glycemic control? Diabetes Care. 2007; 30(1):21-26.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – bilateral peripheral neuropathic pain.
HEMSTREET 2001 Hemstreet B, Lapointe M. Evidence for the use of gabapentin in the treatment of diabetic peripheral neuropathy. Clinical Therapeutics. 2001; 23(4):520-531.	Review article
JENSON 2006 Jensen MP, Friedman M, Bonzo D, Richards P. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. Clinical Journal of Pain. 2006; 22(1):97-103.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy (diabetes type not mentioned)
JOSS 1999 Joss JD. Tricyclic antidepressant use in diabetic neuropathy. Annals of Pharmacotherapy. 1999; 33(9):996-1000.	Review article
KVINESDAL 1985 Kvinesdal B, Molin J, Froland A, Gram LF. Antidepressive agents in the treatment of diabetic neuropathy. Clinical Physiology. 1985; 5(Suppl 5):97-100.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
LAURITZEN 1985 Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. Diabetes. 1985; 34 Suppl 3:74-79.	RCT (SCII vs conventional). Population does not match protocol (type 1 diabetes with retinopathy at start of trial not neuropathy). Wrong outcomes
LOW 1995 Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. Pain. 1995; 62(2):163-168.	Population does not match protocol – chronic neuropathy, only 20% diabetic patients
MAGNUS 2000 Magnus L. Treatment of postherpetic neuralgia and treatment of painful neuropathy in patients with diabetes mellitus: two randomized controlled studies. International Congress and Symposium Series - Royal Society of Medicine. 2000; 241:51-58.	Population does not match protocol - mixed population of type 1 diabetes (~25%) and type 2 diabetes with no subgroup analysis - diabetic peripheral neuropathy.

Reference	Reason for exclusion
MALIK 1998 Malik RA, Williamson S, Abbott C, Carrington AL, Iqbal J, Schady W et al. Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. Lancet. 1998; 352(9145):1978-1981.	Intervention does not match protocol (ACE inhibitor); population does not match protocol - mixed population of type 1 diabetes (65%) and type 2 diabetes with no subgroup analysis – diabetic polyneuropathy.
MARTIN 2006 Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care. 2006; 29(2):340-344.	Intervention does not match protocol (intensive therapy is MDIs or insulin pump)
MAX 1990 (1741) Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. Pain. 1991; 45(1):3-9.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy (diabetes type not mentioned)
MAX 1992 Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. New England Journal of Medicine. 1992; 326(19):1250-1256.	Population does not match protocol - mixed population of insulin-dependent (~60%) and non insulin-dependent with no subgroup analysis – peripheral neuropathy
MCQUAY 1996 McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain. 1996; 68(2-3):217-227.	Review article (included studies mixed populations type 1 diabetes and type 2 diabetes)
MILLER 2012 Miller BHT, Aparnareddy A, Soliman M, Rajbhandari SM. Discontinuation of treatment in patients with painful diabetic peripheral neuropathy. Diabetic Medicine. 2012; 29:121-122.	Abstract only (conference abstract, not a full paper). Wrong population, 15% type 1 diabetes – painful diabetic peripheral neuropathy
MORELLO 1999 (1742) Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Archives of Internal Medicine. 1999; 159(16):1931-1937.	Population does not match protocol - mixed population of insulin-dependent (~65%) and non insulin-dependent with no subgroup analysis - diabetic peripheral neuropathy.
OSKARSSON 1997 (1743) Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. Diabetes Care. 1997; 20(10):1594-1597.	Intervention does not match protocol (anti-arrhythmic). Population does not match protocol – type 1 diabetes and type 2 diabetes with painful diabetic neuropathy.
PASCOE 1997 Pascoe MK, Low PA, Windebank AJ, Litchy WJ. Subacute diabetic proximal neuropathy. Mayo Clinic Proceedings. 1997; 72(12):1123-1132.	Population does not match protocol – not all patients had neuropathy, mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis

Reference	Reason for exclusion
RASKIN 2005 Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine. 2005; 6(5):346-356.	Population does not match protocol - mixed population of type 1 diabetes (~15%) and type 2 diabetes with no subgroup analysis – bilateral peripheral neuropathy.
RASKIN 2006 Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. Journal of Palliative Medicine. 2006; 9(1):29-40.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis– bilateral peripheral neuropathy.
RICHTER 2005A Richter RW, Portenoy R, Sharma U, LaMoreaux L, Bockbrader H, Knapp LE. Relief of painful diabetic peripheral neuropathy with pregabalin: A randomized, placebo-controlled trial. Journal of Pain. 2005; 6(4):253-260.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – distal symmetrical sensorimotor polyneuropathy for 1-5 years.
ROGERS 1994 Rogers DG. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. Clinical Pediatrics. 1994; 33(6):378.	Review article
ROGERS 2004 Rogers LC, Alam U, Malik RA, Tesfaye S. Treatment of painful diabetic neuropathy: A review of the most efficacious pharmacological treatments. Practical Diabetes International. 2004; 21(8):301-306.	Review article
ROWBOTHAM 2004 Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain. 2004; 110(3):697-706.	Population does not match protocol - mixed population of type 1 diabetes (% not reported) and type 2 diabetes with no subgroup analysis – bilateral distal peripheral neuropathy.
RULL 1969 Rull JA, Quibrera R, Gonzalez-Millan H, Lozano CO. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia. 1969; 5(4):215-218.	Population does not match protocol - mixed population of insulin-dependent (~33%) and non insulin-dependent with no subgroup analysis - peripheral neuropathy.
SATOH 2011	Population does not match protocol -

Reference	Reason for exclusion
Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabetic Medicine. 2011; 28(1):109-116.	mixed population of type 1 diabetes (~5%) and type 2 diabetes with no subgroup analysis - symmetrical sensorimotor polyneuropathy.
SAUDEK 1977 Saudek CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. Clinical Pharmacology and Therapeutics. 1977; 22(2):196-199.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
SCHAEPELYNCK 2011 Schaepelynck P, Renard E, Jeandidier N, Hanaire H, Fermon C, Rudoni S et al. A recent survey confirms the efficacy and the safety of implanted insulin pumps during long-term use in poorly controlled type 1 diabetes patients. Diabetes Technology and Therapeutics. 2011; 13(6):657-660.	Population does not match protocol (not all patients had neuropathy)
SCHEFFLER 1991 Scheffler NM, Sheitel PL, Lipton MN. Treatment of painful diabetic neuropathy with capsaicin 0.075%. Journal of the American Podiatric Medical Association. 1991; 81(6):288-293.	Population does not match protocol - mixed population of type 1 diabetes (~60%) and type 2 diabetes with no subgroup analysis – peripheral polyneuropathy.
SEMENCHUK 2001 Semenchuk MR, Sherman S, Davis B. Double-blind, randomized trial of bupropion SR for the treatment of neuropathic pain. Neurology. 2001; 57(9):1583-1588.	Population does not match protocol – chronic neuropathy, not all diabetic patients
SERVICE 1985 Service FJ, Rizza RA, Daube JR, O'Brien PC, Dyck PJ. Near normoglycaemia improved nerve conduction and vibration sensation in diabetic neuropathy. Diabetologia. 1985; 28(10):722-727.	Conventional insulin therapy vs CSII but wrong outcomes (peripheral nerve function). Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
SINDRUP 1990 Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain. 1990; 42(2):135-144.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy
SINDRUP 1992 Sindrup SH, Bjerre U, Dejgaard A, Brosen K, Aaes-Jorgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. Clinical Pharmacology and Therapeutics. 1992; 52(5):547-552.	Population does not match protocol – chronic diabetic neuropathy not insulin-induced neuropathy (diabetes type not mentioned)
SINDRUP 1999 Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain. 1999; 83(3):389-400.	Review article (included studies mixed populations type 1 diabetes and type 2 diabetes)

Reference	Reason for exclusion
SKAER 1999 Skaer TL, Robison LM, Sclar DA, Michael DW, Kozma CM, Eugenc RC. Use of antidepressant pharmacotherapy within the first year after diagnosis of diabetes mellitus: A study of a medicaid population. Current Therapeutic Research, Clinical & Experimental. 1999; 60(8):415-422.	Population does not match protocol (not all patients had neuropathy)
STRACKE 1992 (1746) Stracke H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care. 1992; 15:1550-1555.	Intervention does not match protocol (anti-arrhythmic). Population does not match protocol – mixed population of insulin-dep and non insulin-dep with symptomatic diabetic polyneuropathy.
TANDAN 1992 Tandan R, Lewis GA, Krusinski PB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Controlled study with long-term follow-up. Diabetes Care. 1992; 15(1):8-14.	Population does not match protocol - mixed population of insulin-dependent (~55%) and non insulin-dependent with no subgroup analysis – painful symmetrical diabetic neuropathy.
THE CAPSAICIN STUDY GROUP (ANON 1991) Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group. Archives of Internal Medicine. 1991; 151(11):2225-2229.	Population does not match protocol - mixed population of type 1 diabetes (~50%) and type 2 diabetes with no subgroup analysis
THOMAS 2009A Thomas J. Intensive treatment reduces serious complications in patients with type 1 diabetes mellitus. Australian Journal of Pharmacy. 2009; 90(1074):74.	Comment only (not a full paper)
TOLLE 2008 Tolle T, Freynhagen R, Versavel M, Trostmann U, Young J. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. European Journal of Pain. 2008; 12(2):203-213.	Population does not match protocol - mixed population of type 1 diabetes (~15%) and type 2 diabetes with no subgroup analysis – symmetrical sensorimotor polyneuropathy.
UDELSMAN 2000 Udelsman R, Boyne MS, Loman KE, Saudek CD. Intraperitoneal delivery of insulin via mechanical pump: surgical implications. Langenbeck's Archives of Surgery. 2000; 385(6):367-372.	Does not address the question – pump intervention but not for treatment-induced neuropathy and no comparison group
VANACKER 2009 Van Acker K, Bouhassira D, De Bacquer D, Weiss S, Matthys K, Raemen H et al. Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1	Population does not match protocol (not all patients had neuropathy)

Reference	Reason for exclusion
and type 2 diabetic patients attending hospital outpatients clinics. Diabetes and Metabolism. 2009; 35(3):206-213.	
VERNON 2008 Vernon MK, Brandenburg NA, Alvir JM, Griesing T, Revicki DA. Reliability, Validity, and Responsiveness of the Daily Sleep Interference Scale Among Diabetic Peripheral Neuropathy and Postherpetic Neuralgia Patients. Journal of Pain and Symptom Management. 2008; 36(1):54-68.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis - painful diabetic peripheral neuropathy
VIALA 2008 Viala-Danten M, Martin S, Guillemin I, Hays RD. Evaluation of the reliability and validity of the Medical Outcomes Study sleep scale in patients with painful diabetic peripheral neuropathy during an international clinical trial. Health and Quality of Life Outcomes. 2008; 6.	Population does not match protocol - mixed population of type 1 diabetes (% not reported) and type 2 diabetes with no subgroup analysis - symmetrical sensorimotor polyneuropathy.
WERNICKE 2006 Wernicke JF, Raskin J, Rosen A, Pritchett YL, D'Souza DN, Iyengar S et al. Duloxetine in the long-term management of diabetic peripheral neuropathic pain: An open-label, 52-week extension of a randomized controlled clinical trial. Current Therapeutic Research, Clinical & Experimental. 2006; 67(5):283-304.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis– bilateral peripheral neuropathy.
WERNICKE 2007 Wernicke JF, Wang F, Pritchett YL, Smith TR, Raskin J, D'Souza DN et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. Pain Medicine. 2007; 8(6):503-513.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis– bilateral peripheral neuropathy.
WERNICKE 2009 Wernicke JF, Prakash A, Kajdasz DK, Houston J. Safety and tolerability of duloxetine treatment of diabetic peripheral neuropathic pain between patients with and without cardiovascular conditions. Journal of Diabetes and Its Complications. 2009; 23(5):349-359.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – bilateral peripheral neuropathy.
WILTON 1974 Wilton TD. Tegretol in the treatment of diabetic neuropathy. South African Medical Journal. 1974; 48(20):869-872.	Population does not match protocol - mixed population of insulin-dependent (~8%) and non insulin-dependent with no subgroup – peripheral neuropathy.
WRIGHT 1997 Wright JM, Oki JC, Graves L, III. Mexiletine in the symptomatic treatment of diabetic peripheral neuropathy. Annals of Pharmacotherapy. 1997; 31(1):29-34.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – diabetic polyneuropathy.

Reference	Reason for exclusion
ZHAO 2000 Zhao AX, Lu SQ, Li JL, Yu XE, Li L, Wei DL et al. [Investigation of Lantern Chili for Therapy of Diabetes Mellitus with Peripheral Neuropathy]. Journal of Guangxi Medical University. 2000; 17(5):816-818.	Not in English
ZIEGLER 2007 Ziegler D, Pritchett YL, Wang F, Desaiah D, Robinson MJ, Hall JA et al. Impact of disease characteristics on the efficacy of duloxetine in diabetic peripheral neuropathic pain. Diabetes Care. 2007; 30(3):664-669.	Population does not match protocol - mixed population of type 1 diabetes (~10%) and type 2 diabetes with no subgroup analysis – bilateral peripheral neuropathic pain.
WERNICKE 2006 J. F. Wernicke, J. Raskin, A. Rosen, Y. L. Pritchett, D. N. D'Souza, S. Iyengar, K. Knopp, and T. K. Le. Duloxetine in the long-term management of diabetic peripheral neuropathic pain: An open-label, 52-week extension of a randomized controlled clinical trial. Curr.Ther.Res.Clin.Exp. 67 (5):283-304, 2006.	Mixed population of type 1 diabetes and type 2 diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis. Already excluded in original review.
ALLEN 2014 R. Allen, U. Sharma, and S. Barlas. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. *J.Pain Res.* 7:339-351, 2014.	Wrong population: diabetic peripheral neuropathy.
ANG 2014 Lynn Ang, Mamta Jaiswal, Catherine Martin, and Rodica Pop-Busui. Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 14 (9):528, 2014.	Review article. Used as source of references.
BOYLE 2012 J. Boyle, M. E. Eriksson, L. Gribble, R. Gouni, S. Johnsen, D. V. Coppini, and D. Kerr. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes care* 35 (12):2451-2458, 2012.	Already found study in pre-rerun literature. Has been excluded from the review due to wrong population: mixed type 1 diabetes and type 2 diabetes.
CALLAGHAN 2012 Brian C. Callaghan, Ann A. Little, Eva L. Feldman, and A. C. Hughes Richard. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* Issue 6:CD007543, 2012.	Already found study in pre-rerun literature. Has been excluded from the review due to wrong intervention (not match protocol).
MERANTE 2014 D. Merante, U. Sharma, K. Feins, C. Hsu, and A. I. Vinik. Efficacy of DS-5565 in diabetic peripheral neuropathic pain: Pain assessment and correlations with a numerical rating scale and visual analog	Conference abstract

Reference	Reason for exclusion
scale. *Diabetes* 63:A144, 2014.	
SMITH 2014 T. Smith, A. Dibernardo, Y. Shi, M. J. Todd, H. R. Brashear, and L. M. Ford. Efficacy and safety of carisbamate in patients with diabetic neuropathy or postherpetic neuralgia: Results from 3 randomized, double-blind placebo-controlled trials. *Pain Pract.* 14 (4):332-342, 2014.	Wrong population: diabetic peripheral neuropathy.
VINIK 2014 A. I. Vinik, D. Y. Shapiro, C. Rauschkolb, B. Lange, K. Karcher, D. Pennett, and M. S. Etropolski. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes care* 37 (8):2302-2309, 2014.	Wrong population: chronic (not acute) diabetic neuropathy.

K.10.3 Thyroid disease-frequency of monitoring

Reference	Reason for exclusion
Abaci A, Bober E, Yesilkaya E, Bideci A, Cinaz P, Buyukgebiz A. Prevalence of anticardiolipin antibodies in type 1 diabetes and autoimmune thyroiditis. Polskie Archiwum Medycyny Wewnetrznej. 2010; 120(3):71-75	Wrong population: children
Adrees M, Boran G. Subclinical hypothyroidism. CPD Bulletin Clinical Biochemistry. 2002; 4(3):67-70	Narrative review
Aksoy DY, Yurekli BPS, Yildiz BO, Gedik O. Prevalence of glutamic acid decarboxylase antibody positivity and its association with insulin secretion and sensitivity in autoimmune thyroid disease: A pilot study. Experimental and Clinical Endocrinology and Diabetes. 2006; 114(8):412-416	Wrong population: not type 1 diabetes
Alexander CM, Kaptein EM, Lum SMC, Spencer CA, Kumar D and Nicoloff JT. Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus. Journal of Clinical Endocrinology and Metabolism. 1982;54 (2):362-366	Small study size
Al Saidi SS, Al Harthi SO, Mula-Abed W-AS. Diagnostic utility of coeliac disease: a descriptive study in a tertiary care hospital, oman. Oman Medical Journal. 2013; 28(4):232-236	Wrong testing: no testing for thyroid disease
Alexopoulou O, Jamart J, Maiter D, Hermans MP, De Hertogh R, De Nayer P et al. Erectile dysfunction and lower androgenicity in type 1 diabetic patients. Diabetes and Metabolism. 2001; 27(3):329-336	Wrong population: does not include thyroid disease
Alver A, Mentese A, Karahan SC, Erem C, Keha EE, Arikan MK et al. Increased serum anti-carbonic anhydrase II antibodies in patients with Graves' disease. Experimental and Clinical Endocrinology and Diabetes. 2007; 115(5):287-291	Wrong population: does not include type 1 diabetes

Reference	Reason for exclusion
Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? Autoimmune Diseases. 2012; 2012:251730.	Narrative review
Araujo J, Brandao LAC, Guimaraes RL, Santos S, Falcao EA, Milanese M et al. Prevalence of autoimmune thyroid disease and thyroid dysfunction in young Brazilian patients with type 1 diabetes. Pediatric Diabetes. 2008; 9(4 Pt 1):272-276	Wrong population age: children and adolescents
Awata T, Kawasaki E, Tanaka S, Ikegami H, Maruyama T, Shimada A et al. Association of type 1 diabetes with two Loci on 12q13 and 16p13 and the influence coexisting thyroid autoimmunity in Japanese. Journal of Clinical Endocrinology and Metabolism. 2009; 94(1):231-235	Wrong test: association of gene loci of type 1 diabetes and thyroid disease
Badenhoop K. Immunogenetic markers for autoimmune diseases of the endocrine system. Klinische Wochenschrift. 1990; 68(SUPPL. 21):10-14	Wrong test: HLA-DQ and TNF genetic polymorphisms
Badenhoop K, Boehm BO. Genetic susceptibility and immunological synapse in type 1 diabetes and thyroid autoimmune disease. Experimental and Clinical Endocrinology and Diabetes. 2004; 112(8):407-415	Narrative review
Badenhoop K, Kahles H, Ramos-Lopez E, Boehm B. Both isolated type 1 diabetes and polyautoimmune beta cell failure of APS2 share the same susceptibility profile at gene loci: HLA DR, CTLA4, and INS in the T1DGC dataset. Diabetologia. 2009; 52(S1):S110	Conference abstract
Bajwa SJS, Jindal R. Endocrine emergencies in critically ill patients: Challenges in diagnosis and management. Indian Journal of Endocrinology and Metabolism. 2012; 16(5):722-727.	Management of diabetes and thyroid disease as separate diseases, not combined
Bakker SF, Tushuizen ME, Von Blomberg ME, Mulder CJ, Simsek S. Type 1 diabetes and celiac disease in adults: Glycemic control and diabetic complications. Acta Diabetologica. 2013; 50(3):319-324	Type 1 diabetes not with thyroid disease
Bardella MT, Elli L, Matteis SD, Floriani I, Torri V, Piodi L. Autoimmune disorders in patients affected by celiac sprue and inflammatory bowel disease. Annals of Medicine. 2009; 41(2):139-143	Wrong condition:coeliac disease, Crohn's disease, ulcerative colitis
Bardymova T, Kolesnichenko L, Sergeeva E, Verlan N, Sergeeva M. Glutathione antioxidant protection in patients with diabetes mellitus. Atherosclerosis. 2009; 10(S2).	Conference abstract
Barker JM. Type 1 diabetes-associated autoimmunity: Natural history, genetic associations, and screening. Journal of Clinical Endocrinology and Metabolism. 2006; 91(4):1210-1217.	Wrong age: Children
Barker JM, Yu J, Yu L, Wang J, Miao D, Bao F et al. Autoantibody "subspecificity" in type 1 diabetes: risk for organ-specific autoimmunity clusters in distinct groups. Diabetes Care. 2005; 28(4):850-855.	Narrative review

Reference	Reason for exclusion
Barnard M, Tzoulis P. Diabetes and thalassaemia. Thalassemia Reports. 2013; 3(1 SUPPL.):49-53.	No information on diabetes type
Bensing S, Jonsson P, Hulting A-L, Cook D, Gordon M, Faust M et al. Lymphocytic hypophysitis: Clinical characteristics and endocrine features of 64 GH deficient patients in KIMS: Pfizer International Metabolic Database. Endocrine Abstracts. 2010; 22:619.	Conference abstract
Betterle C, Zanchetta R. Update on autoimmune polyendocrine syndromes (APS). Acta Biomedica De L'Ateneo Parmense. 2003; 74(1):9-33.	Narrative review
Bizzaro N. Autoantibodies as predictors of disease: The clinical and experimental evidence. Autoimmunity Reviews. 2007; 6(6):325-333	Narrative review
Bizzaro N. The predictive significance of autoantibodies in organ-specific autoimmune diseases. Clinical Reviews in Allergy and Immunology. 2008; 34(3):326-331.	Narrative review
Blomhoff A, Lie BA, Myhre AG, Kemp EH, Weetman AP, Akselsen HE et al. Polymorphisms in the cytotoxic T lymphocyte antigen-4 gene region confer susceptibility to Addison's disease. Journal of Clinical Endocrinology and Metabolism. 2004; 89(7):3474-3476.	Wrong condition and test: genetic susceptibility to Addison's disease
Boitard C, Feutren G, Castano L, Debray-Sachs M, Assan R, Hors J et al. Effect of cyclosporin A treatment on the production of antibody in insulin-dependent (type I) diabetic patients. Journal of Clinical Investigation. 1987; 80(6):1607-1612.	No information about TSH levels or T3 and T4 in study
Booy JD, Takata J, Tomlinson G, Urbach DR. The prevalence of autoimmune disease in patients with esophageal achalasia. Diseases of the Esophagus. 2012; 25(3):209-213.	Population not type 1 diabetes and thyroid disease
Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004; 89(10):1187-1193.	Wrong age: children*
Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Annals of the New York Academy of Sciences. 2004; 1032:141-153.	Wrong population: not type 1 diabetes and thyroid disease
Bosi E, Andreotti AC, Girardi AM, Bottazzo GF, Pozza G. The long-term persistence of islet cell antibodies in Type I diabetic patients is unrelated to residual beta-cell function. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 1991; 4(4):319-323.	Wrong population: not type 1 diabetes and thyroid disease
Botero LE, Toro AE, Patino AJ, Salazar G, Rodriguez JC, Suarez-Escudero JC et al. Diabetes mellitus in patients with Alzheimer's disease: clinical description and correlation with the APOE genotype in a sample population from the province of Antioquia, Colombia. Biomedica. 2012; 32(2):239-251.	Type of diabetes not described

Reference	Reason for exclusion
Boudraa G, Bouziane-Nedjadi K, Bessahraoui M, Naceur M, Hachelaf W, Touhami M. Type 1 diabetes-celiac disease association. Clinical and evolutive aspects. Pediatric Diabetes. 2011; 12:48-49.	Conference abstract
Breen L, Thomas S, Doherty E, Powrie J, Brackenridge A, Carroll P. Long-term consequences of auto-immune primary adrenal failure. Endocrine Abstracts. 2009; 19:323.	Conference abstract
Bright GM. Quantitative assay for human cytoplasmic islet cell antibodies. Diabetes. 1987; 36(10):1183-1186.	Diagnostic
Brooking H, Ananieva-Jordanova R, Arnold C, Amoroso M, Powell M, Betterle C et al. A sensitive non-isotopic assay for GAD65 autoantibodies. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2003; 331(1-2):55-59.	Diagnostic: type 1 diabetes and thyroid disease tested separately
Brown TL, Sippl RM, Snell-Bergeon JK. Healthy pre-monopausal women with type 1 diabetes have increased peripheral Insulin resistance compared to non-diabetic women. Diabetes. 2012; 61:A447.	Conference abstract
Bulum T, Duvnjak L, Car N. Insulin sensitivity modifies the relationship between thyroid function and lipid profile in euthyroid type 1 diabetic patients. Diabetes. 2011; 60:A190.	Conference abstract
Bulum T, Kolaric B, Duvnjak L. Insulin sensitivity modifies the relationship between thyroid function and lipid profile in euthyroid type 1 diabetic patients. Endocrine. 2012; 42(1):139-145.	**Check,
Burbelo PD, Lebovitz EE, Bren KE, Bayat A, Paviol S, Wenzlau JM et al. Extrapancreatic autoantibody profiles in type I diabetes. PloS One. 2012; 7(9):e45216.	Wrong population: Children
Calvert GM, Sweeney MH, Deddens J, Wall DK. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Occupational and Environmental Medicine. 1999; 56(4):270-276.	Type of diabetes not reported
Carreras 2007	Letter
Casale M, Citarella S, Filosa A, De ME, Pugliese U, Francesco P et al. Long term efficacy of iron chelation therapy with deferasirox on endocrine function in thalassemia major. Blood. 2013; 122(21).	Conference abstract
Casey R, Eddie A, Bell M, Dineen B. Investigation of screening standards for thyroid dysfunction and celiac disease in type 1 diabetes in the west of, Ireland. Endocrine Reviews. 2011; 32(3 Meeting Abstracts).	Conference abstract
Casey R, Eddie A, Bell M, Dineen B. The prevelance of hypothyroidism and celiac disease in patients with type 1 diabetes in the west of Ireland. Endocrine Reviews. 2011; 32(3 Meeting Abstracts).	Conference abstract

Reference	Reason for exclusion
Cats EA, Bertens AS, Veldink JH, van den Berg LH, van der Pol WL. Associated autoimmune diseases in patients with multifocal motor neuropathy and their family members. Journal of Neurology. 2012; 259(6):1137-1141.	Wrong population: multifocal motor neuropathy
Cen H, Wang W, Leng RX, Wang TY, Pan HF, Fan YG et al. Association of IFIH1 rs1990760 polymorphism with susceptibility to autoimmune diseases: a meta-analysis. Autoimmunity. 2013; 46(7):455-462.	Meta -analysis of genetic association of IFIH1rs1990760 polymorphism
Ch'ng CL, Jones MK, Kingham JGC. Celiac disease and autoimmune thyroid disease. Clinical Medicine and Research. 2007; 5(3):184-192.	Population not type 1 diabetes
Choudhary N, Chikkaveerappa K, Underwood P, Leong KS. Thyroxine replacement precipitating adrenal crisis. Endocrine Abstracts. 2009; 19:64.	Conference abstract
Cleemann L, Oftedal B, Trolle C, Holm K, Husebye ES, Gravholt CH. 21-hydroxylase and interferon omega autoantibodies in Turner syndrome. Hormone Research in Paediatrics. 2013; 80:85.	Conference abstract
Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. Journal of Allergy and Clinical Immunology. 2012; 129(5):1307-1313.	Chronic uticaria, type 1 diabetes and thyroid disease separate groups, no information on thyroid hormone or antibody levels
Cooper GS, Miller FW, Pandey JP. The role of genetic factors in autoimmune disease: implications for environmental research. Environmental Health Perspectives. 1999; 107 Suppl 5:693-700.	Narrative review
Cortese A, Di BC, Pontecorvo S, Di RS, Millefiorini E, Francia A et al. Multiple sclerosis and other autoimmune disorders: A common susceptibility? Multiple Sclerosis. 2009; 15(9 Suppl. S):S160-S161.	Conference abstract
Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. American Journal of Human Genetics. 2005; 76(4):561-571.	Phenotype association of two genes
Cruz AAV, Akaishi PMS, Vargas MA, de Paula SA. Association between thyroid autoimmune dysfunction and non-thyroid autoimmune diseases. Ophthalmic Plastic and Reconstructive Surgery. 2007; 23(2):104-108.	Not type 1 diabetes and thyroid
Collin 1994	Wrong population: Coeliac disease, type 1 diabetes and thyroid disease separate groups
Danieli MG, Rossetti L, Fraticelli P, Malcangi G, Testa I, Danieli G. Autoimmune thyroid diseases in patients with undifferentiated connective tissue disease. Clinical Rheumatology. 2000; 19(1):42-46.	Wrong population: not type 1 diabetes
De Block CEM, De Leeuw IH, Pelckmans PA, Callens D, Maday E, Van Gaal LF. Delayed gastric emptying and gastric autoimmunity in type 1 diabetes.	Data split into subgroup and not type 1 diabetes as whole

Reference	Reason for exclusion
Diabetes Care. 2002; 25(5):912-917.	
de Graaff LCG, Smit JWA, Radder JK. Prevalence and clinical significance of organ-specific autoantibodies in type 1 diabetes mellitus. Netherlands Journal of Medicine. 2007; 65(7):235-247.	Narrative review
De Remigis P, Vianale L, De RA, Napolitano G. Vitamin d and autoimmune thyroid disease (at): Preliminary results. Thyroid. 2013; 23:A81-A82.	Conference abstract
Deretzi G, Kountouras J, Koutlas E, Zavos C, Polyzos S, Rudolf J et al. Familial prevalence of autoimmune disorders in multiple sclerosis in Northern Greece. Multiple Sclerosis. 2010; 16(9):1091-1101.	Check*
Diez JJ, Iglesias P, Selgas R. Pituitary dysfunctions in uremic patients undergoing peritoneal dialysis: a cross sectional descriptive study. Advances in Peritoneal Dialysis Conference on Peritoneal Dialysis. 1995; 11:218-224.	Diabetes type not reported
Dizdarevic-Bostandic A, Burekovic A, Velija-Asimi Z, Godinjak A. Inflammatory markers in patients with hypothyroidism and diabetes mellitus type 1. Medicinski Arhiv. 2013; 67(3):160-161.	Wrong markers reported:HBAc1
Djilali-Saiah I, Bertin E, Larger E, Timsit J, Assan R, Boitard C et al. Major histocompatibility class II genes polymorphism in insulin dependent diabetes mellitus with or without associated thyroid autoimmunity. Human Immunology. 1998; 59(3):176-182.	Wrong markers reported:HLA
Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. American Journal of Psychiatry. 2006; 163(3):521-528.	type 1 diabetes and thyroid disease reported as separate groups
Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. Multiple Sclerosis. 2004; 10(5):575-581.	Wrong population:MS
El Hefnawy MH, Bassyouni A, Abdel-Kareem M, Abdel RN, Aziz M, Emara I. Evaluation of subclinical thyroiditis among Egyptian type 1 diabetic patients. Pediatric Diabetes. 2011; 12:108.	Conference abstract
Erichsen MM, Lovas K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. Journal of Clinical Endocrinology and Metabolism. 2009; 94(12):4882-4890.	Wrong population:Addison's disease
Einarsdottir E, Soderstrom I, Lofgren-Burstrom A, Haraldsson S, Nilsson-Ardnor S, Penha-Goncalves C et al. The CTLA4 region as a general autoimmunity factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease. European Journal of Human Genetics. 2003; 11(1):81-84	Wrong marker:CTLA-5 Genetic pedigree study

Reference	Reason for exclusion
Ferrer A, Padros G, Formiga F, Rojas-Farreras S, Perez JM, Pujol R. Diabetes mellitus: prevalence and effect of morbidities in the oldest old. The Octabaix study. Journal of the American Geriatrics Society. 2012; 60(3):462-467.	Diabetes type not reported
Flatau E, Trougouboff P, Kaufman N, Reichman N, Luboshitzky R. Prevalence of hypothyroidism and diabetes mellitus in elderly kibbutz members. European Journal of Epidemiology. 2000; 16(1):43-46.	Wrong population:type 2 diabetes
Frasier SD, Penny R, Snyder R, Goldstein I, Graves D. Antithyroid antibodies in Hispanic patients with type I diabetes mellitus. Prevalence and significance. American Journal of Diseases of Children. 1986; 140(12):1278-1280.	Wrong age:children and adolescents
Gamberini MR, Fortini M, De Sanctis V, Gilli G, Testa MR. Diabetes mellitus and impaired glucose tolerance in thalassaemia major: incidence, prevalence, risk factors and survival in patients followed in the Ferrara Center. Pediatric Endocrinology Reviews. 2004; 2 Suppl 2:285-291.	Wrong age: children
Gamberini MR, De Sanctis V, Gilli G. Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: incidence and prevalence related to iron overload and chelation therapy in patients with thalassaemia major followed from 1980 to 2007 in the Ferrara Centre. Pediatric Endocrinology Reviews. 2008; 6 Suppl 1:158-169.	Wrong age:children
Gardner R, Mahadev S, Lebwohl B, Tennyson CA, Green PH, Lewis SK. Quality of life in patients with celiac disease detected by screening vs. Celiac disease detected by symptoms. Gastroenterology. 2013; 144(5 SUPPL. 1):S755.	Conference abstract
Gherbon A, Noveanu L, Mihalas G. Prevalence of chronic autoimmune thyroiditis in a group of adults with diabetes mellitus and other changes in glycemic balance. Pancreatology. 2012; 12(6):515.	Conference abstract
Golden B, Levin L, Ban Y, Concepcion E, Greenberg DA, Tomer Y. Genetic analysis of families with autoimmune diabetes and thyroiditis: evidence for common and unique genes. Journal of Clinical Endocrinology and Metabolism. 2005; 90(8):4904-4911.	Wrong markers:HLA and DR3-DQB1, genetic susceptibility
Gonzalez GC, Capel I, Rodriguez-Espinosa J, Mauricio D, de Leiva A, Perez A. Thyroid autoimmunity at onset of type 1 diabetes as a predictor of thyroid dysfunction. Diabetes Care. 2007; 30(6):1611-1612.	
Greene S, Goring S, Cochrane L, Donnan P, Bell A, Heather D et al. The clinical and economic burden of type 1 diabetes in children, adolescents and adults. Pediatric Diabetes. 2011; 12:26.	Conference abstract
Hafler JP, Maier LM, Cooper JD, Plagnol V, Hinks A, Simmonds MJ et al. CD226 Gly307Ser association with multiple autoimmune diseases. Genes and Immunity. 2009; 10(1):5-10.	Wrong markers: CD226 Gly307Ser: Genetic association

Reference	Reason for exclusion
Hill PG, McMillan SA. Anti-tissue transglutaminase antibodies and their role in the investigation of coeliac disease. Annals of Clinical Biochemistry. 2006; 43(2):105-117.	Review, Coeliac disease
Lamberts LE, Janse M, Haagsma EB, Van Den Berg AP, Weersma RK. Immune-mediated diseases in primary sclerosing cholangitis. Gastroenterology. 2011; 140(5 SUPPL. 1):S919.	Conference abstract
Lamberts LE, Janse M, Haagsma EB, van den Berg AP, Weersma RK. Immune-mediated diseases in primary sclerosing cholangitis. Digestive and Liver Disease. 2011; 43(10):802-806.	Wrong population:primary sclerosing cholangitis
Lestringant GG, Bener A, Frossard P, Townsend A. Association of Acanthosis nigricans with risk of diabetes mellitus and hormonal disturbances in females. International Journal of Gynaecology and Obstetrics: the Official Organ of the International Federation of Gynaecology and Obstetrics. 2000; 71(3):267-269.	Mixed age of population: 16-65, proportion not reported Type of diabetes not reported
Lipworth L, Zucchetto A, Bosetti C, Franceschi S, Talamini R, Serraino D et al. Diabetes mellitus, other medical conditions and pancreatic cancer: A case-control study. Diabetes/Metabolism Research and Reviews. 2011; 27(3):255-261.	Majority children with pancreatic cancer, type of diabetes not reported
Ludvigsson JF, Kampe O, Lebwohl B, Green PHR, Silverberg SJ, Ekbom A. Primary hyperparathyroidism and celiac disease: a population-based cohort study. Journal of Clinical Endocrinology and Metabolism. 2012; 97(3):897-904.	Population not type 1 diabetes +thyroid
Makinen V-P, Forsblom C, Thorn LM, Waden J, Kaski K, Ala-Korpela M et al. Network approach to type 1 diabetes: association patterns between diabetic complications and metabolic, clinical and life style risk factors in a set of 4197 patients. Diabetologia. 2009; 52(S1):S383.	Conference abstract
MClaren 2012	Conference abstract
McLeod 2012	Narrative review, incidence and prevalence of worldwide thyroid disease
Medaoud S, Hakem D, Ouadahi N, Boudjelida A, Hamadane A, Baba-Ahmad R et al. Megaloblastic anaemia: Clinical and biological profiles. European Journal of Neurology. 2009; 16(S3):568.	
Mehta RL, Davies MJ, Ali S, Taub NA, Stone MA, Baker R et al. Association of cardiac and non-cardiac chronic disease comorbidity on glycaemic control in a multi-ethnic population with type 1 and type 2 diabetes. Postgraduate Medical Journal. 2011; 87(1033):763-768.	Population either type 1 diabetes or type 2 diabetes, thyroid disease not defined/reported
Michalek AM, Mahoney MC, Calebaugh D. Hypothyroidism and diabetes mellitus in an American Indian population. Journal of Family Practice. 2000; 49(7):638-640.	Diabetes type not reported

Reference	Reason for exclusion
Mollazadegan K, Kugelberg M, Tallstedt L, Ludvigsson JF. Increased risk of uveitis in coeliac disease: a nationwide cohort study. British Journal of Ophthalmology. 2012; 96(6):857-861.	Population not type 1 diabetes
Mortensen KH, Cleemann L, Hjerrild BE, Nexo E, Locht H, Jeppesen EM et al. Increased prevalence of autoimmunity in Turner syndrome--influence of age. Clinical and Experimental Immunology. 2009; 156(2):205-210.	Type 1 diabetes and thyroid as separate groups
Osborne E, Braffett B, Dunn RL, Kim C, Cleary P, Cowie C et al. Self-reported autoimmune disease by gender in the epidemiology of diabetes intervention and complications (EDIC) Study. Diabetes. 2012; 61:A390-A391.	Conference abstract
Patel C, Singh V. Underlying diseases and other gastrointestinal abnormalities in patients with Celiac disease. Pediatric and Developmental Pathology. 2010; 13(2):143.	Conference abstract
Penna-Martinez M, Ramos-Lopez E, Robbers I, Kahles H, Hahner S, Willenberg H et al. The rs1990760 polymorphism within the IFIH1 locus is not associated with Graves' disease, Hashimoto's thyroiditis and Addison's disease. BMC Medical Genetics. 2009; 10.	Genetic polymorphism, not type 1 diabetes
Pittock SJ, Yoshikawa H, Ahlskog JE, Tisch SH, Benarroch EE, Kryzer TJ et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. Mayo Clinic Proceedings. 2006; 81(9):1207-1214.	Wrong population: MS and pancreatic cancer Wrong marker:GAD65
Procaccini E, Chianelli M, Pantano P, Signore A. Imaging of autoimmune diseases. Quarterly Journal of Nuclear Medicine. 1999; 43(1):100-112.	Narrative review
Qorbani M, Bazrafshan HR, Aghaei M, Dashti HS, Rezapour A, Asayesh H et al. Diabetes mellitus, thyroid dysfunctions and osteoporosis: is there an association? Journal of Diabetes and Metabolic Disorders. 2013; 12(1):38.	Population:osteoporosis Diabetes type unclear
Riley WJ, Toskes PP, Maclaren NK, Silverstein JH. Predictive value of gastric parietal cell autoantibodies as a marker for gastric and hematologic abnormalities associated with insulin-dependent diabetes. Diabetes. 1982; 31(12):1051-1055.	Wrong population: Children Not type 1 diabetes and thyroid disease
Sherif EM, Farid SM, Toaima DN, El Kabarity RH. Demographic characteristics and autoimmunity in familial type 1 diabetes. Pediatric Diabetes. 2012; 13:81.	Conference abstract
Sheth VM, Guo E, Qureshi AA. Co-morbidities associated with Vitiligo: A 10-year retrospective study. Journal of Investigative Dermatology. 2012; 132(7):1941.	Population not type 1 diabetes and thyroid disease
Sheth VM, Guo Y, Qureshi AA. Comorbidities associated with vitiligo: a ten-year retrospective study. Dermatology. 2013; 227(4):311-315.	Conference abstract

Reference	Reason for exclusion
Shiau MY, Tsai ST, Hwang J, Wu CY, Chang YH. Relationship between autoantibodies against glutamic acid decarboxylase, thyroglobulin/thyroid microsome and DNA topoisomerase II in the clinical manifestation of patients with type 1 diabetes mellitus in Taiwan. European Journal of Endocrinology. 2000; 142(6):577-585.	Population not type 1 diabetes and thyroid
Signore A, Picarelli A, Annovazzi A, Britton KE, Grossman AB, Bonanno E et al. 123I-Interleukin-2: biochemical characterization and in vivo use for imaging autoimmune diseases. Nuclear Medicine Communications. 2003; 24(3):305-316.	Diagnostic, wrong marker :Interleukin-2
Simunkova K, Hampl R, Hill M, Kriz L, Hrda P, Janickova-Zdarska D et al. Adrenocortical function in young adults with diabetes mellitus type 1. Journal of Steroid Biochemistry and Molecular Biology. 2010; 122(1-3):35-41.	Results divided up into different subgroups of adrenal function rather than type 1 diabetes together
Sridhar GR, Nagamani G. Clinical association of autoimmune diseases with diabetes mellitus: analysis from southern India. Annals of the New York Academy of Sciences. 2002; 958:390-392.	Diabetes type not reported, no information on thyroid tests
Starup-Linde J, Vestergaard P, Karlstad O, Eriksen SA, Bronsveld HK, De VF et al. Caring: Diabetes mellitus and risk of cancer-a systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety. 2013; 22:402-403.	Conference abstract
Taniyama M, Kasuga A, Nagayama C, Ito K. Occurrence of type 1 diabetes in Graves' disease patients who are positive for antiglutamic acid decarboxylase antibodies: An 8-year followup study. Journal of Thyroid Research. 2011; 2011.	Not sure
Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nature Genetics. 2007; 39(7):857-864.	Genetic association of type 1 diabetes and Graves' disease, no information about thyroid tests
Toh BH, Kyaw T, Taylor R, Pollock W, Schlumberger W. Parietal cell antibody identified by ELISA is superior to immunofluorescence, rises with age and is associated with intrinsic factor antibody. Autoimmunity. 2012; 45(7):527-532.	Wrong marker: Parietal cell antibody
Tomer Y, Barbesino G, Keddache M, Greenberg DA, Davies TF. Mapping of a major susceptibility locus for Graves' disease (GD-1) to chromosome 14q31. Journal of Clinical Endocrinology and Metabolism. 1997; 82(5):1645-1648.	Population not type 1 diabetes
Tomer Y, Davies TF. Searching for the Autoimmune Thyroid Disease Susceptibility Genes: From Gene Mapping to Gene Function. Endocrine Reviews. 2003; 24(5):694-717.	Narrative review
Torfs CP, King M-C, Huey B. Genetic interrelationship between insulin-dependent diabetes mellitus, autoimmune thyroid diseases, and rheumatoid arthritis. American Journal of Human Genetics. 1986; 38(2):170-187.	Age of participants not reported, genetic linkage of type 1 diabetes and thyroid disease genes
Tremlett HL, Evans J, Wiles CM, Luscombe DK. Asthma and multiple	Wrong population: MS,

Reference	Reason for exclusion
sclerosis: an inverse association in a case-control general practice population. QJM. 2002; 95(11):753-756.	Asthma
Tryfonopoulos D, Anastasiou E, Protogerou A, Papaioannou T, Lily K, Dagre A et al. Arterial stiffness in type 1 diabetes mellitus is aggravated by autoimmune thyroid disease. Journal of Endocrinological Investigation. 2005; 28(7):616-622.	Not sure
Tseng CH. Thyroid cancer risk is not increased in diabetic patients. PloS One. 2012; 7(12):e53096.	Type of diabetes unclear
Tseng CH. Diabetes and thyroid cancer mortality: a 12-year prospective follow-up of Taiwanese. European Journal of Clinical Investigation. 2013; 43(6):595-601.	Type of diabetes unclear
Tsurumaru M, Kawasaki E, Ida H, Migita K, Moriuchi A, Fukushima K et al. Evidence for the role of small ubiquitin-like modifier 4 as a general autoimmunity locus in the Japanese population. Journal of Clinical Endocrinology and Metabolism. 2006; 91(8):3138-3143.	Wrong marker: SUMO4 locus for genetic susceptibility, study looked at gene variation
Usman J, Siddiqui H. Osteoporosis in Family Practice. Journal of the Pakistan Medical Association. 2003; 53(9):433-436.	Wrong population:osteoporosis
Vaidya B, Imrie H, Perros P, Young ET, Kelly WF, Carr D et al. Evidence for a new Graves disease susceptibility locus at chromosome 18q21. American Journal of Human Genetics. 2000; 66(5):1710-1714.	Wrong study type: Genetic linkage of chromosome 18q21 for Grave's disease and also type 1 diabetes
van Belzen MJ, Mulder CJJ, Zhernakova A, Pearson PL, Houwen RHJ, Wijmenga C. CTLA4 +49 A/G and CT60 polymorphisms in Dutch coeliac disease patients. European Journal of Human Genetics. 2004; 12(9):782-785.	Population not type 1 diabetes
Van der Auwera BJ, Vandewalle CL, Schuit FC, Winnock F, De Leeuw IH, Van IS et al. CTLA-4 gene polymorphism confers susceptibility to insulin-dependent diabetes mellitus (IDDM) independently from age and from other genetic or immune disease markers. Clinical and Experimental Immunology. 1997; 110(1):98-103.	Wrong marker: CTLA4 gene polymorphism in type 1 diabetes
Villano MJ, Huber AK, Greenberg DA, Golden BK, Concepcion E, Tomer Y. Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. Journal of Clinical Endocrinology and Metabolism. 2009; 94(4):1458-1466.	Wrong marker: genetic susceptibility genes for type 1 diabetes and thyroid disease
Vojdani A. Antibodies as predictors of complex autoimmune diseases. International Journal of Immunopathology and Pharmacology. 2008; 21(2):267-278.	Diagnostic antibody tests, type 1 diabetes and thyroid disease tested as separate groups
Walikonis JE, Lennon VA. Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clinic Proceedings. 1998; 73(12):1161-1166.	type 1 diabetes and thyroid disease reported as separate groups rather than together

Reference	Reason for exclusion
Warncke K, Frohlich-Reiterer EE, Thon A, Hofer SE, Wiemann D, Holl RW. Polyendocrinopathy in children, adolescents, and young adults with type 1 diabetes: A multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database. Diabetes Care. 2010; 33(9):2010-2012.	Wrong population age: children
Wiebe JC, Santana A, Hernandez M, Novoa J, Mauricio D, Wagner AM. Predictors of associated autoimmune diseases in families with type 1 diabetes. Results from the type 1 diabetes genetics consortium (T1DGC). Diabetologia. 2009; 52(S1):S17.	Conference abstract
Yamaguchi K, Fukushima H, Uzawa H. Response of human growth hormone, prolactin and thyrotropin to thyrotropin releasing hormone in liver cirrhosis and diabetes mellitus. Endocrinologia Japonica. 1979; 26(1):81-88.	Diabetes type not defined
Yamashita H, Awata T, Kawasaki E, Ikegami H, Tanaka S, Maruyama T et al. Analysis of the HLA and non-HLA susceptibility loci in Japanese type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2011; 27(8):844-848.	Wrong marker:HLA
Zhebrun D, Kudryashova Y, Babenko A, Maslyansky A, Kunitskaya N, Popcova D et al. Association of PTPN22 1858T/T genotype with type 1 diabetes, Graves' disease but not with rheumatoid arthritis in Russian population. Aging. 2011; 3(4):368-373.	Age of population not clear Genetic susceptibility of PTPN22 gene
Agarwal K, Jones DE, Daly AK, James OF, Vaidya B, Pearce S et al. CTLA-4 gene polymorphism confers susceptibility to primary biliary cirrhosis. Journal of Hepatology. 2000; 32(4):538-541.	type 1 diabetes and thyroid disease as separate groups rather than together Wrong marker:CTLA4
Akamine H, Komiya I, Shimabukuro T, Asawa T, Tanaka H, Yagi N et al. High prevalence of GAD65 (and IA-2) antibodies in Japanese IDDM patients by a new immunoprecipitation assay based on recombinant human GAD65. Diabetic Medicine. 1997; 14(9):778-784.	Wrong population age: children
Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Medicine. 1998; 15(7):539-553.	Report: classification of DM
Amed S, Nuernberger K, McCrea P, Reimer K, Krueger H, Aydede SK et al. Adherence to clinical practice guidelines in the management of children, youth, and young adults with type 1 diabetes--a prospective population cohort study. Journal of Pediatrics. 2013; 163(2):543-548.	Population type 1 diabetes only, mixed ages 1-24 years, proportions not reported
Bain SC, Gill GV, Dyer PH, Jones AF, Murphy M, Jones KE et al. Characteristics of Type 1 diabetes of over 50 years duration (the Golden Years Cohort). Diabetic Medicine. 2003; 20(10):808-811.	Population type 1 diabetes only
Betterle C, Zanette F, Pedini B, Presotto F, Rapp LB, Monciotti CM et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1	Population age ranged from 2-67years for diabetic group,

Reference	Reason for exclusion
(insulin-dependent) diabetic patients and their first-degree relatives. Diabetologia. 1984; 26(6):431-436.	10-63 years for relatives group, and 2-71 years for normal group. Age proportions in each group not clear
Bhatia E, Mehra NK, Malaviya AN, Ahuja MM. HLA and autoimmunity in North Indian type I (insulin-dependent) diabetic multiplex families. Hormone and Metabolic Research. 1986; 18(5):331-334.	Wrong population: children
Binus AM, Han J, Qamar AA, Mody EA, Holt EW, Qureshi AA. Associated comorbidities in psoriasis and inflammatory bowel disease. Journal of the European Academy of Dermatology and Venereology. 2012; 26(5):644-650.	type 1 diabetes and thyroid disease reported as separate groups rather than together
Bottazzo GF, Foulis AK, Bosi E, Todd I, Pujol-Borrell R. Pancreatic beta-cell damage. In search of novel pathogenetic factors. Diabetes Care. 1988; 11 Suppl 1:24-28.	Narrative review
Bower RS, Mallory GW, Nwojo M, Kudva YC, Flemming KD, Meyer FB. Moyamoya disease in a primarily white, midwestern US population: increased prevalence of autoimmune disease. Stroke; a Journal of Cerebral Circulation. 2013; 44(7):1997-1999.	Population not clearly defined as type 1 diabetes or type 2 diabetes
Bower WF, Jin L, Underwood MJ, Lee JF, Lee KF, Lam YH et al. Overt diabetes mellitus adversely affects surgical outcomes of noncardiovascular patients. Surgery. 2010; 147(5):670-675.	Population: type 1 diabetes and thyroid disease reported as separate groups rather than together
Collins JE, Heward JM, Nithiyananthan R, Nejentsev S, Todd JA, Franklyn JA et al. Lack of association of the vitamin D receptor gene with Graves' disease in UK Caucasians. Clinical Endocrinology. 2004; 60(5):618-624.	Wrong marker: association of vitamin D gene with Grave's disease
De Bellis A, Bizzarro A, Amoresano Paglionico V, Di Martino S, Criscuolo T, Sinisi AA et al. Detection of vasopressin cell antibodies in some patients with autoimmune endocrine diseases without overt diabetes insipidus. Clinical Endocrinology. 1994; 40(2):173-177.	Population: type 1 diabetes and thyroid disease reported as separate groups No information on thyroid tests
Dultz G, Matheis N, Dittmar M, Bender K, Kahaly GJ. CTLA-4 CT60 polymorphism in thyroid and polyglandular autoimmunity. Hormone and Metabolic Research. 2009; 41(6):426-429.	Population: type 1 diabetes and thyroid disease reported as separate groups Wrong marker: CTLA4 gene for susceptibility
Hamza RT, Raof NA, Abdallah KO. Prevalence of multiple forms of autoimmunity in Egyptian patients with Turner syndrome: relation to karyotype. Journal of Pediatric Endocrinology and Metabolism. 2013; 26(5-6):545-550.	Population: Turner syndrome type 1 diabetes and thyroid disease reported as separate groups Majority population children
Hegewald MJ, Schoenfeld SL, McCulloch DK, Greenbaum CJ, Klaff LJ, Palmer JP. Increased specificity and sensitivity of insulin antibody measurements in autoimmune thyroid disease and type I diabetes. Journal of Immunological Methods. 1992; 154(1):61-68.	Diagnostic assay for identification of insulin antibodies Age of population not clear Population: type 1 diabetes and thyroid disease reported

Reference	Reason for exclusion
	as separate groups
Kasperlik-Zaluska AA, Czarnocka B, Czech W, Walecki J, Makowska AM, Brzezinski J et al. Secondary adrenal insufficiency associated with autoimmune disorders: a report of twenty-five cases. Clinical Endocrinology . 1998; 49(6):779-783.	Population not type 1 diabetes
Koumakis E, Dieude P, Avouac J, Kahan A, Allanore Y, Association des Sclerodermiques de France. Familial autoimmunity in systemic sclerosis -- results of a French-based case-control family study. Journal of Rheumatology. 2012; 39(3):532-538.	Population: Systemic sclerosis
Li Voon Chong JSW, Leong KS, Wallymahmed M, Sturgess R, MacFarlane IA. Is coeliac disease more prevalent in young adults with coexisting Type 1 diabetes mellitus and autoimmune thyroid disease compared with those with Type 1 diabetes mellitus alone? Diabetic Medicine. 2002; 19(4):334-337.	Mixed age of population (16-55 years), age proportions not clear Data for type 1 diabetes group not reported Thyroid disease tests not reported
Perros P, Singh RK, Ludlam CA, Frier BM. Prevalence of pernicious anaemia in patients with Type 1 diabetes mellitus and autoimmune thyroid disease. Diabetic Medicine. 2000; 17(10):749-751.	Prevalence of pernicious anaemia
Schlosser K, Maschuw K, Hassan I, Karakas E, Sebastian H, Slater EP et al. Are diabetic patients at a greater risk to develop a vocal fold palsy during thyroid surgery than nondiabetic patients? Surgery. 2008; 143(3):352-358.	Diabetes type unclear Vocal fold palsy as a result of thyroid surgery in diabetes patients
Tomar N, Gupta N, Goswami R. Calcium-sensing receptor autoantibodies and idiopathic hypoparathyroidism. Journal of Clinical Endocrinology and Metabolism. 2013; 98(9):3884-3891.	Wrong marker: CaSR antibody Age of population unclear type 1 diabetes and thyroid disease reported as separate groups rather than together
Ventura A, Neri E, Ughi C, Leopaldi A, Citta A, Not T. Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. Journal of Pediatrics. 2000; 137(2):263-265.	Population age: children
Yagura T, Ishii H, Yoshimasa T, Ohnishi T, Yonemoto T, Hamada S. Multivariable analysis of serum 3,5,3'-L-triiodothyronine concentration in patients of diabetes mellitus by blood glucose level and body weight. Hormone and Metabolic Research. 1990; 22(4):237-240.	Diabetes type not clear
Zhang D, Zhou Z, Li L, Weng J, Huang G, Jing P et al. Islet autoimmunity and genetic mutations in Chinese subjects initially thought to have Type 1B diabetes. Diabetic Medicine. 2006; 23(1):67-71.	Wrong marker: genetic mutations in HNF1a gene in type 1 diabetes
Goswami R, Marwaha RK, Goswami D, Gupta N, Ray D. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. Journal of Clinical Endocrinology and Metabolism. 2006; 91(11): 4256-4259.	Type 1 diabetes and thyroid disease reported as separate groups rather than together
Okosieme OE, Wijeyaratne CN, Lazarus JH, Premawardhana LDKE. Restricted thyroglobulin antibody epitope specificities in subjects with type	Type 1 diabetes and thyroid disease reported as separate

Reference	Reason for exclusion
1 diabetes mellitus. European Journal of Endocrinology. 2009; 161:489-493.	groups rather than together
Kesani M, Aronow WS, Weiss MB. Prevalence of multivessel coronary artery disease in patients with diabetes mellitus without hypothyroidism, and in patients with no diabetes mellitus or hypothyroidism. Journals of Gerontology. 2003; 587-588.	Diabetes type not defined
Dittmar M and Kahaly GJ. Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. Journal of Endocrinology and Metabolism. 2003; 88(7):2983-2992.	Type 1 diabetes and thyroid disease reported as separate groups rather than together
Fichna M, Fichna P, Gryczynska M, Walkowiak J, Zurawek M, Sowinksi J. Screening for associated autoimmune disorders in Polish patients with Addison's disease. Endocrine. 2010; 37(2): 349-360.	Type 1 diabetes and thyroid disease reported as separate groups rather than together
Gray RS, Borsey DQ, Irvine WJ, Seth J and Clarke BF. Natural history of thyroid function in diabetics with impaired thyroid reserve: a four year controlled study. Clinical Endocrinology. 1983; 19:445-451.	Diabetes type not clearly defined
Hanukoglu A, Mirachi A, Dalal I, Admoni O, Roakover Y, Bistritzer Z, Levine A, Somekh E, Lehmann D, Tuval M, Boaz M, Golander A. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives. Diabetes care. 2003; 26(4):1235-1240.	Population <18 years age at diagnosis
Silva RC, Sallorenzo C, Kater CE, Dib SA, Falorni A. Autoantibodies against glutamic acid decarboxylase and 21-hydroxylase in Brazilian patients with type 1 diabetes or autoimmune thyroid diseases. Diabetes Nutrition and Metabolism. 2003; 16:160-168.	Type 1 diabetes and thyroid disease as separate groups rather than together
Murao S, Kondo S, Ohashi J, Fujii Y, Shimizu I, Fujiyama M, Ohno K, Takada Y, Nakai K, Yamane Y, Osawa H, Makina H. Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict beta cell failure in patients with latent autoimmune diabetes in adults (LADA)-a 5-year follow-up of the Ehime study. Diabetes Research and Clinical Practice. 2008; 80:114-121.	Unclear grouping of population, no information on thyroid testing Wrong marker-c-peptide
Lindholm E, Hallengren B, Agardh C-D. Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. Diabetes/Metabolism Research and Reviews. 2004; 20:158-164.	Wrong marker-c-peptide, no measurement of thyroid disease
Kirkgaard C, Norgaard K, Snorgaard O, Bek T, Larsen M and Lund-Anderson H. Effect of one -year continuous subcutaneous infusion of a somatostatin analogue, octreotide, on early retinopathy, metabolic control and thyroid function in type 1 (insulin-dependent) diabetes mellitus. Acta Endocrinologica. 1990; 122:766-772.	Data for control group not reported
Ditta A, Tayyab M, Chaudhry NA, Qavi A, Malik MA. Significance of thyrotropin and thyroxine estimations I type 1 diabetes.	Mixed population age, children and adults in one group

Reference	Reason for exclusion
Duntas L, Keck FS, Wolf CH, Hauner H, Pfeiffer EF. Thyrotropin-releasing hormone degradation in patients with insulin dependent diabetes mellitus. Effects of metabolic control. Thyroidology. 1991; 3:51-57.	Population size too small-8 T1d and 6 control
Vondra K, Vrbikova J, Bendlova B, Dvorakova K, Sterzl I, Vondrova M. Differences in type 1 diabetes mellitus of young adults with and without thyroid autoimmunity. Experimental and Clinical Endocrinology. 2005; 113:404-408.	Wrong marker-c-peptide No data for thyroid dysfunction
Somers EC, Thomas SL, Smeeth L, Hall AJ. Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? American Journal of Epidemiology. 2009; 169(6); 749-755.	Type 1 diabetes and thyroid disease as separate groups rather than together
Hamada N, Ito T, Mimura T, Momotani N, Nishikawa Y, Fujii S, Morii H, Wada M. Factors predicting the course of diabetes mellitus in hyperthyroid patients. Hormone and Metabolic Research. 1986; 18:260-263.	Diabetes type not clear
Riley WJ, Winer A, Goldstein D. Coincident presence of thyro-gastric autoimmunity at onset of type 1 (insulin-dependent) diabetes. Diabetologia. 1983; 24:418-421.	Data for thyroid disease markers not clear
Tryfonopoulos D, Anastasiou E, Protogerou A, Papaioannou T, Lily K, Dagre A, Souvatzoglou E, Papamichael C, Alevizaki M, Lekakis J. Arterial stiffiness in type 1 diabetes mellitus is aggravated by thyroid disease. Journal of Endocrinological Investigation. 2005; 28:616-622.	No data for thyroid disease markers
Taniyama M, Kasuga A, Nagayama, Ito K. Occurrence of type 1 diabetes in Grave's disease patients who are positive for antiglutamic acid decarboxylase antibodies: an 8 year follow-up study. Journal of Thyroid research. 2011; 2011;1-4.	Wrong marker:GADA
Davis RE, McCann VJ, Stanton KG. Type 1 diabetes and latent pernicious anaemia. The medical journal of Australia. 1992; 156:160-162.	Diabetes onset<18 years age
Goni MJ, Monreal M, Goni F, Sopena M, Gil MJ, Moncada E, Salvador J. Effects of cholinergic blockade on nocturnal thyrotropin and growth hormone (GH) secretion in type 1 diabetes mellitus: further evidence supporting somatostatin's involvement in GH suppression. Metabolism. 1997; 46(11):1305-1311.	Duration of study too short: 7 hours
Plewe G, Nolken G, Krause U, Del Pozo E, Beyer J. Somatostatin analogue SMS 201-995 in type 1 diabetes. Initial experience after repeated administration. Scandinavian Journal of Gastroenterology. 1986; 21(suppl 119):166-169.	Wrong marker: glucose, duration of monitoring too short: hours
Giampietro O, Ferdeghini M, Cerri M, Cecere M, Uncini-Manganelli C, Ruberti F, Matteucci E. Evaluation of the hypothalamic-pituitary-testicular interaction in diabetic males. European Journal of Laboratory Medicine. 1993; 2(2):83-89.	Only baseline thyroid markers, not monitored over time
Groop LC, Bottazzo GF, Doniach D. Islet cell antibodies identify latent type I	Wrong tests for monitoring:

Reference	Reason for exclusion
diabetes in patients aged 35-75 years at diagnosis. Diabetes. 1986; 35(2):237-241	islet cell antibodies
Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. Journal of Autoimmunity. 2007; 29(1):1-9.	Prevalence of autoimmune diseases as a group, no testing for thyroid antibodies or hormones
Cardenas-Roldan J, Rojas-Villarraga A, Anaya JM. How do autoimmune diseases cluster in families? A systematic review and meta-analysis. BMC Medicine. 2013; 11:73.	Does not look at thyroid disease in type 1 diabetes patients, type 1 diabetes and thyroid disease assessed separately
Kabadi UM, Premachandra BN, Maayan M. Low serum 3, 5, 3'-triiodothyronine (T3) and raised 3, 3', 5'-triidothyronine (reverse T3 or RT3) in diabetes mellitus: normalization on improvement in hyperglycemia. Acta Diabetologica Latina. 1982; 19(3):233-242.	Thyroid hormone concentration and relationship with blood glucose levels, not concentration in the whole group
Pittman CS, Suda AK, Chambers J. Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. Journal of Clinical Endocrinology and Metabolism. 1979; 48(5):854-860.	Very small study number of n=8
Kota SK, Meher LK, Jammula S, Kota SK, Modi KD. Clinical profile of coexisting conditions in type 1 diabetes mellitus patients. Diabetes and Metabolic Syndrome. 2012; 6(2):70-76.	Wrong population=children
Macfarlane IA, Sheppard MC, Black EG, Gilbey S, Wright AD. The hypothalamic-pituitary-thyroid axis in type 1 diabetes: influence of diabetic metabolic control. Acta Endocrinologica. 1984; 106(1):92-96.	Study number very small n=8
UECKERMANN 2013 V. Ueckermann and D. G. Van Zyl. The prevalence of subclinical hypothyroidism among patients with diabetes mellitus at the Kalafong Hospital Diabetes Clinic: A cross-sectional study. *J.Endocrinol.Metab.Diabetes S.Afr.* 18 (2):106-110, 2013.	Mixed population of type 1 diabetes and type 2 diabetes; <70% type 1 diabetes and no type 1 diabetes subgroup analysis.
ABOSMAHA 2014 E. A. Abosmaha, S. E. Almsahli, S. G. Alsabri, S. S. Mohamed, and M. Gebreil. Coexistence of autoimmune disease with type I diabetes mellitus in Libyan patients. *Int.J.Pharmcy Pharm.Sci.* 6 (2):120-124, 2014.	Wrong population: mixed ages of children, young people and adults. No subgroup analysis of adults, and % of adult unclear.
DIZDARAVIC 2013 A Dizdarevic-Bostandic, Azra Burekovic, Zelija Velija-Asimi, and Amina Godinjak. Inflammatory markers in patients with hypothyroidism and diabetes mellitus type 1. *Med Arh* 67 (3):160-161, 2013.	Already found study in pre-rerun literature. Was excluded due to loking at the wrong amrkers, not those pre-specified in our protocol.
GOUVEIA 2013 S. Gouveia, L. Gomes, C. Ribeiro, and F. Carrilho. Screening for autoimmune polyglandular syndrome in a cohort of patients with type 1 diabetes mellitus. *Arq Bras Endocrinol Metabol* 57 (9):733-738, 2013.	Not written in English.

Reference	Reason for exclusion
MILENKOVC 2013 T. Milenkovic, S. Todorovic, K. Mitrovic, D. Zdravkovic, I. Kitic, L. Plavsic, and R. Vukovic. Additional autoimmune diseases in patients with type 1 diabetes mellitus at diagnosis of diabetes. *Pediatr.Diabetes* 14:127, 2013.	Conference abstract
RODACKI 2014 M. Rodacki, L. Zajdenverg, J. R. Dantas, R. A. Cobas, J. E. P. Oliveira, R. R. Luiz, C. A. Negrato, and M. B. Gomes. TSH levels are associated with the risk of diabetic retinopathy and renal failure in patients with type 1 diabetes. *Diabetes* 63:A90, 2014.	Conference abstract

Appendix L: Excluded economic studies

Reference	Reason for exclusion
deWeerdt 1991[120]	Selectively excluded on the basis of the availability of a UK CUA
Trento 2005[494]	Selectively excluded on the basis of the availability of a UK CUA
Elliott 2014[139]	Selectively excluded as it was less applicable and had more limitations compared to the included study.
Shearer 2004 [457]	Selectively excluded as this was updated by a more recent analysis[268]
[170]	Selectively excluded as it was less applicable and had more limitations compared to the included study.
Newman 2009[367] [UK]	This study was excluded as it was a cost-analysis that was performed alongside a trial of a mixed population of patients with type 1 and type 2 diabetes, with an 18 month time horizon.
Davey 1998 [114] [CAN]	This study has been selectively excluded due to the methodological limitations of willingness to pay studies and the availability of superior evidence from the UK.
Reviriego 2008 [429] [ESP]	This study has been selectively excluded as it only considers the impact on hypoglycaemia and as such does not take all health outcomes into account.
Guillermin 2011[188] [Canada]	This study was excluded due to methodological limitations as the study analysed the cost difference between insulin glargine and insulin detemir and did not consider quality-of-life.
Valentine2012 [503] [Nordic]	This study was excluded due to methodological limitations as this study assesses the short term effects of mild hypoglycaemia event reduction. As such, it does not include all important health effects in the long term.
Ericsson 2013[140]	This study assesses the short term effects of hypoglycaemia event reduction. As such, it does not include all important health effects in the long term.
DCCT Group [491]	This was included in the previous guideline but does not look at the correct intervention.
Palmer 2000[391]	This was included in the previous guideline but does not look at the correct intervention for this review and contains a mixed population of type 1 and type 2 diabetes patients.
Wu 1998[530]	This was included in the previous guideline but does not look at the correct intervention for this review and contains a mixed population of type 1 and type 2 diabetes patients.
Dranitsaris 2000[132]	This was included in the previous guideline but does not look at the correct intervention for this review question.
Davey 1998[114]	This was included in the previous guideline but does not look at the correct intervention for this review question.
Herman 1997[205]	This was included in the previous guideline but is only a cost analysis does not look at the correct intervention for this review question.
Stern 1996[478]	This was included in the previous guideline but does not look at the correct intervention for this review question.
Hannon 2011[194]	This study was assessed as partially applicable with very serious limitations. It was a within-group comparison where admission costs were assessed for four patients before and after they had the intervention. The comparator is unclear. The cost of the intervention itself was not reported and/or not included.

Appendix M: Network meta-analysis: long-acting insulin

M.1 Overview of network meta-analysis methods

We conducted a network meta-analysis (NMA) of the efficacy of long-acting insulin regimens. The studies included within the review formed two networks of evidence for the critical outcomes identified by the GDG, that is, a separate network is developed for each of the two outcomes: HbA1c, and severe/major hypoglycaemia.

All the studies included in the clinical review of long-acting insulin and once versus twice insulin regimens (n=29) were assessed for inclusion in the NMA. Studies were included if they reported usable data on the outcomes of interest and the effect measure. Twenty eight studies were considered suitable for inclusion in the NMA, as one study[230] did not report change in HbA1c levels and reported no severe or major hypoglycaemic events in both arms. Of these; 25 studies, of nine interventions, were included in the HbA1c network (as three studies of the 28 either did not report the change in HbA1c for the relevant comparison, did not report its standard deviation or it was not possible to calculate these from the data) and 16 studies, of eight interventions, were included in the severe/major hypoglycaemia network (as five studies did not report severe/major hypoglycaemia as an outcome, four studies did not report the number of severe/major hypoglycaemic episodes or its rate and three studies reported no severe/major hypoglycaemic events in both arms of the trial). For details of the included studies, see Table 63.

In the main clinical review of long acting insulin, the study results were pooled together, regardless of regimen, however; a subgroup analysis considering frequency of administration was also conducted. In the NMA, the studies have been separated out based on regimen (for example, once, twice or four times daily) where this was clear in the study. Some studies of insulin NPH and insulin detemir, however, used a mix of regimens (specifically once and twice daily) in the same arm and it was not possible to separate the data for each regimen. To take this into account, we included two regimens that represented combination of once and twice daily administrations of insulin NPH and insulin detemir in the analysis. This was decided to ensure that the NMA uses all relevant trials and data.

Accordingly, the following insulin regimens were included in the NMA:

NPH (once or twice daily)

NPH (once daily)

NPH (twice daily)

NPH (four times daily)

Detemir (once or twice daily)

Detemir (once daily)

Detemir (twice daily)

Glargine (once daily)

Degludec (once daily)

Study data for the first outcome, reduction in HbA1c, were combined regardless of follow-up time; however, short-term results of less than four weeks were excluded as the GDG considered that HbA1c and the occurrence of severe/major hypoglycaemia would not change in this time. In the analysis of severe/major hypoglycaemia outcome data, follow-up time was taken into account where the outcome measure used was the rate of severe/major hypoglycaemic events per person year of follow up.

Pairwise meta-analysis results for the direct comparisons of these outcomes in the included studies are also presented here; as the clinical review used different criteria as explained above. The interventions and studies included in each network are shown in Table 63 below. A summary of the results of the NMA are reported in section M.4.3 . For a more detailed explanation of the methodology and of the results of the NMA, refer to section M.4.

Table 63: Interventions and studies included in the network meta-analysis

Study	Outcomes	
	HbA1c	Severe or major hypoglycaemia
GLARGINE (Once Daily) versus NPH (Twice Daily)		
CHATTERJEE 2007[84]	Not Reported	✓
DEREMIR (Twice Daily) versus NPH (Twice Daily)		
HOME 2004[218 a]	✓	✓
PIEBER 2005[407]	✓	✓
LEEUW 2005[287]	✓	✓[b]
STANDL 2004[473]	✓	✓
VAGUE 2003[500]	✓	✓
HERMANSEN 2004[206]	✓	✓
HERMANSEN 2001[207]	Not Reported	✓
KOLENDORF 2006[263]	✓	✓
GLARGINE (Once Daily) versus DETEMIR (Once Daily)		
RENARD 2011[427]	✓	✓
HELLER 2009[202c]	✓	Not Reported
GLARGINE (Once Daily) versus DETEMIR (twice Daily)		
HELLER 2009[202c]	✓	Not Reported
GLARGINE (Once Daily) versus NPH (Four Times Daily)		
PORCELLATI 2004[410]	✓	✓[d]
ROSSETTI 2003[439]	✓	✓[d]
GLARGINE (Once Daily) versus DEGLUDEC (Once Daily)		
BIRKELAND 2011[55] and HOME 2012[221]	✓	Not Reported
MATHIEU 2013 [310]	✓	✓
HELLER 2012[201]	✓	✓
GLARGINE (Once Daily) versus NPH (Once Daily)		
FULCHER 2005[156]	✓[e]	✓
GLARGINE (Once Daily) vs NPH (Once or Twice Daily)		
BOLLI 2009[60]	✓	Not Reported
RASKIN 2000[417]	✓	✓
RATNER 2000[420]	✓	✓

ROSENSTOCK 2000[437]	✓	Not Reported
HOME 2005[218]	✓	✓[b]
PIEBER 2000[408]	✓	✓[b]
GLARGINE (Once Daily) vs DETEMIR (Once or Twice Daily)		
HELLER 2009[202c]	Not Reported[c]	✓
DETEMIR (Once Daily) versus DETEMIR (Twice Daily)		
HELLER 2009[202]	✓	Not Reported
LE FLOCH 2009[281]	✓	Not Reported
DETEMIR (Once Daily) versus NPH (Once Daily)		
RUSSELL-JONES 2004[441]	✓	✓
GOLEN 2013[174]	✓	Not reported
NPH (Once or Twice Daily) versus DETEMIR (Once or Twice Daily)		
ZACHARIAH 2011[536]	✓	✓[d]
BARTLEY 2008[48]	✓	✓

(a) Only data from the clinically relevant regimen of insulin detemir (twice daily), administered morning and bed time, were used.

(b) These studies did not report the rate of severe/major hypoglycaemic events per person year or sufficient data to allow its calculation and therefore cannot be used to estimate rate ratios. They were therefore omitted from the WinBUGS code.

(c) Three arm trial informing four comparisons as the severe/major hypoglycaemia data were presented combined for the insulin detemir (once and twice daily) arm while the results for HbA1c were reported separately for each of the insulin detemir regimens.

(d) These studies reported 0 severe hypoglycaemic events in both arms and therefore cannot be used to estimate rate ratios.

(e) Standard deviation (SD) not reported.

M.2 Network meta-analysis details

M.2.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the long acting insulin review and once versus twice daily review) do not help inform the answer to the question of which is the most effective long-acting insulin for the treatment of type 1 diabetes. The challenge of interpretation has arisen for three reasons:

1. No trial compares all the relevant comparators
2. In isolation, each pair-wise comparison does not inform the choice among the different long-acting insulin treatments.
3. In addition, direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (insulin degludec versus. insulin NPH).

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions based on efficacy[127]. In this case efficacy was defined as the change in HbA1c and time to first severe/major hypoglycaemic event.

The analysis also provided estimates of effect (with 95% credible intervals, the Bayesian equivalent of confidence intervals) for each. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates are required to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared with another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials[126].

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on participants in trials of intervention A compared with intervention B as it does for participants in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on[126].

This method is also referred to as mixed-treatment comparisons analysis.

M.3 Methods

M.3.1 Study selection and data collection

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on RCTs with a follow up time of no less than four weeks. All of the dosages of drugs in the included RCTs were within the therapeutic range as advised by the GDG. All of the studies were in adults only.

M.3.2 Outcome measures

The possible clinical efficacy outcomes identified from the clinical evidence review included: HbA1c, severe hypoglycaemia, major hypoglycaemia, hypoglycaemia, DKA, change in body weight, injection site issues, injection site pain, adverse events, serious adverse events and quality of life. Only HbA1c and severe/major hypoglycaemia were included as outcome measures for the NMA, as they were frequently reported across the studies, whereas the other outcomes were not. The GDG also considered that HbA1c and severe/major hypoglycaemia were the most important (critical) clinical outcomes for assessing the efficacy of long-acting insulin treatment. Change in body weight was not included in the analysis as it was not considered to be a critical outcome in type 1 diabetes (in contract to type 2 diabetes).

Outcome measures were calculated using the numbers as reported by the authors, which was where possible on an available case basis (that is, the analysis was based on the number of participants analysed in each study). The mean treatment effect is defined in the HbA1c network as reduction from baseline compared with the insulin NPH (twice daily). In the severe/major hypoglycaemia network, the treatment effect was defined as the rate of severe/major hypoglycaemic events measured as the number of events/episodes per person year or follow-up time.

M.3.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in the long acting insulin and once versus twice insulin review. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded. It should be acknowledged that the interventions in this network meta-analysis are also differentiated by the number of administrations daily.

Possible confounding variables included the type of rapid-acting bolus insulin used at meal-times and the length of treatment which differed between trials. The GDG advised that the variation among trials in the type of rapid-acting bolus insulin used at meal-times is unlikely to confound the results, as long as within the same trial the same type of rapid-acting insulin is used in both arms. In all included trials, the same rapid-acting bolus insulin was used in both trial arms. The difference in follow-up time has been controlled for in the clinical review by grouping studies into two groups: one with follow-up of less than 6 months and one with follow-up of more than 6 months. In the NMA, different trial follow up times were taken into account when analysing the data; where the rate of severe/major hypoglycaemic events per person year was used as the outcome measure.

M.3.4 Mean treatment effect (HbA1c)

Insulin NPH (twice daily) was chosen as the baseline comparator as this is the 'standard' human long-acting insulin. To calculate baseline mean treatment effect, a single arm meta-analysis of the studies of insulin NPH (twice daily) in the HbA1c network of evidence in RevMan was conducted.

Using this method produced a mean change in HbA1c of -0.32 (95% CI: -0.49, -0.15) when using insulin NPH (twice daily).

M.3.5 Baseline rate (severe/major Hypoglycaemia)

The baseline rate of severe/major hypoglycaemia is defined here as the number of severe/major hypoglycaemic events per person year of follow up when using NPH (twice daily). Deriving this figure from our randomised controlled trials involved calculating a weighted average of severe/major hypoglycaemic events rate in the NPH (twice daily) arms of the studies included in our NMA

Using this method produced baseline rate severe/major hypoglycaemic events of 0.46 events per person year when using NPH (twice daily).

M.3.6 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS 1.4.3. We adapted multi-arm fixed and random effects model templates from the NICE Decision Support Unit (DSU) technical support document TSD2[126]. These models account for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome, a diagram of the evidence network was produced - see section M.4.

The model used for the "change in HbA1c" outcome was based on a random effects logistic regression, with parameters estimated by Markov chain Monte Carlo (MCMC) simulation. As it was a Bayesian analysis; for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. The priors for the differences in HbA1c were normally distributed with a mean of zero and standard deviation of 100.

When modelling an outcome such as the rate of severe/major hypoglycaemic events, it is important to consider the different follow-up times of the various trials, as longer follow-up is likely to result in more reported events. To account for this, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a log link function used to model the event rate.

For both analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history, kernel density plots, and Brooks-Gelman Rubin plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the sum of the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well. Both analyses were attempted both as fixed and random effect models and the Deviance Information Criterion (DIC) compared.

The aims of the NMAs were to calculate the change in HbA1c and the rate of severe/major hypoglycaemic events per patient year for each treatment. The results, in terms of mean difference (for change in HbA1c) and rate ratios (for severe/major hypoglycaemic events) are presented in the results section. We also calculated the overall ranking of interventions according to their effect sizes by counting the proportion of simulations of the Markov chain in which each intervention had the highest reduction in HbA1c and the lowest severe/major hypoglycaemic events rate.

A key assumption behind NMA is that the network is consistent. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

Different populations (for example, age, baseline HbA1c)

Different interventions (doses, regimen)

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed using Bucher's test[128].

M.4 Results

A total of 28 studies from the original evidence review met the inclusion criteria for the NMA. Twenty five studies were included in the HbA1c network, and 16 in the severe/major hypoglycaemia network. All of the included studies were in adults only.

For the HbA1c network, the 25 studies, published in 26 papers, generated 27 different comparisons (see Table 64). This is because one study was 3-arm trial (published in two papers (BIRKELAND 2011[55] and HOME 2012[221])) looking at two different doses of insulin degludec versus glargine. It generated two comparisons. A second study (Heller 2009) generated 3 comparisons because it conducted a subgroup analysis of different administration frequencies of insulin treatments: insulin glargine (once daily) versus insulin detemir (twice daily), insulin glargine (once daily) versus insulin detemir (once daily) and insulin detemir (once daily) versus insulin detemir (twice daily).

In the severe/major hypoglycaemia network, 16 studies published in 16 papers generated 16 comparisons (see Table 65). Insulin NPH (four times daily) was not included in this network as both of the studies relating to this regimen reported no severe/major hypoglycaemic events in both arms.

Figure 255 and Figure 256 show the networks created by eligible comparisons for the NMA, with numbers on the connecting lines indicating the number of studies for each comparison. We report the results for all nine interventions in the network including insulin NPH (once or twice) and detemir (once or twice) for completion, however, the basal insulin regimens of interest that were included in the economic model are those with the deifned frequency of admisnitation to inform a recommendation regarding both the type and the frequency of administration of long acting insulin.

Figure 255: Network for HbA1c

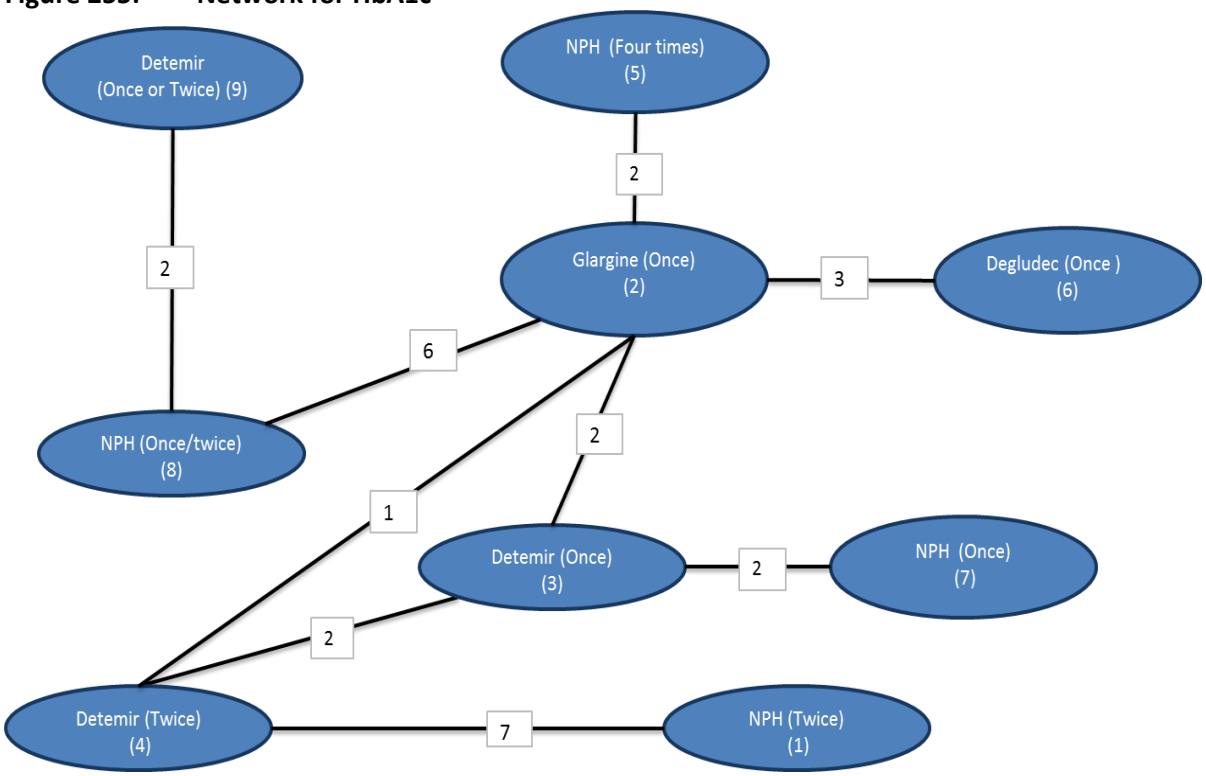


Figure 256: Network for severe/major hypoglycaemia

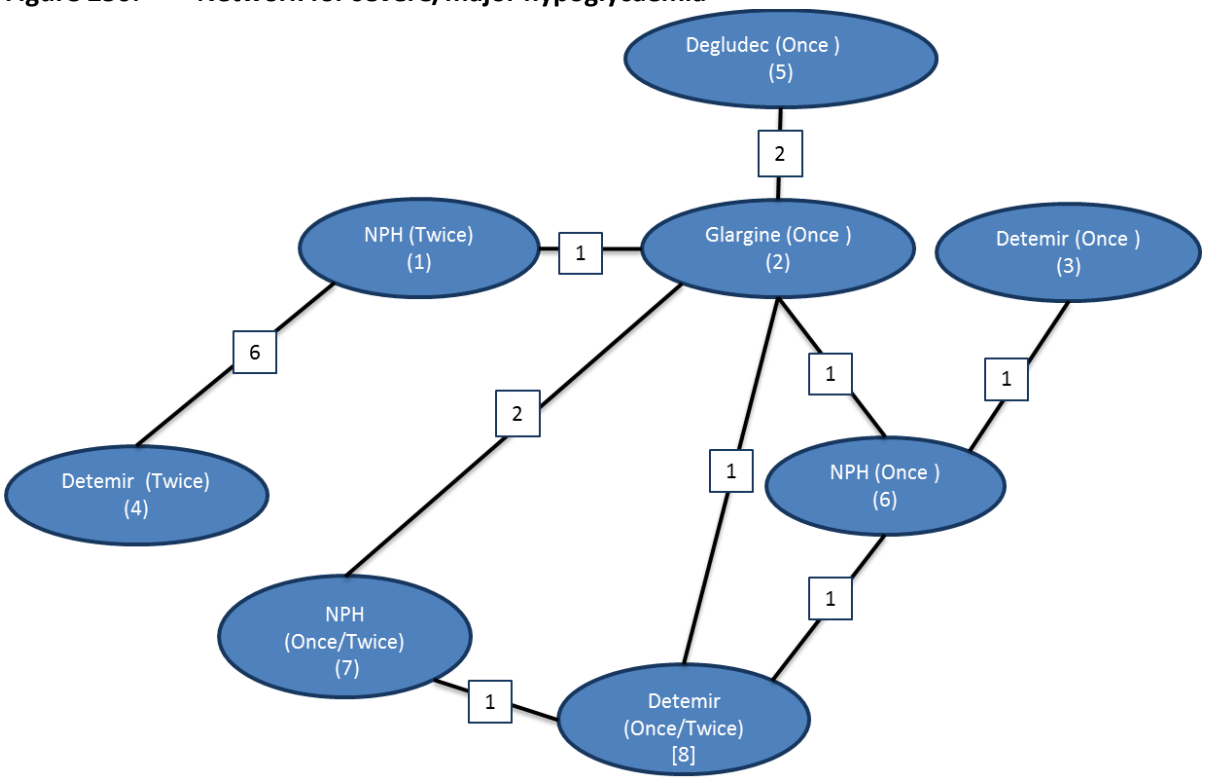


Table 64: Study data for HbA1c

Study	Comparator 1	Comparator 2	Comparator 1		Comparator 2	
			Mean	SE	Mean	SE
HOME 2004[218]	NPH (twice daily)	Detemir (twice daily)	-0.65	0.07	-0.82	0.07
KOLENDORF 2006[263]	NPH (twice daily)	Detemir (twice daily)	-0.30	0.06	-0.30	0.06
LEEUW 2005[287]	NPH (twice daily)	Detemir (twice daily)	-0.44	0.12	-0.65	0.09
STANDL 2004[473]	NPH (twice daily)	Detemir (twice daily)	0.12	0.10	0.16	0.09
VAGUE 2003[500]	NPH (twice daily)	Detemir (twice daily)	-0.47	0.10	-0.58	0.09
HERMANSEN 2004[206]	NPH (twice daily)	Detemir (twice daily)	-0.18	0.05	-0.60	0.05
PIEBER 2005[407]	NPH (twice daily)	Detemir (twice daily)	-0.35	0.09	-0.48	0.10
RENARD 2011[427]	Glargine (once daily)	Detemir (once daily)	-0.19	0.05	-0.20	0.09
HELLER 2009[202]	Glargine (once daily)	Detemir (once daily)	-0.54	0.06	-0.49	0.05
HELLER 2009[202]	Glargine (once daily)	Detemir (twice daily)	-0.54	0.06	-0.58	0.06
BIRKELAND 2011[55] + HOME	Glargine (once daily)	Degludec (once daily)	-0.62	0.09	-0.57	0.10

Study	Comparator 1	Comparator 2	Comparator 1		Comparator 2	
			Mean	SE	Mean	SE
2012[221]						
BIRKELAND 2011[55] + HOME 2012[221]	Glargine (once daily)	Degludec (once daily)	-0.62	0.09	-0.54	0.09
HELLER 2012[201]	Glargine (once daily)	Degludec (once daily)	-0.39	0.07	-0.40	0.03
MATHIEU 2013[310]	Glargine (once daily)	Degludec (once daily)	-0.58	0.06	-0.41	0.06
PORCELLATTI 2004[410]	Glargine (once daily)	NPH (four times daily)	-0.40	0.01	0.00	0.02
ROSSETTI 2003[439]	Glargine (once daily)	NPH (four times daily)	-0.40	0.17	0.10	0.10
BOLLI 2009[60]	Glargine (once daily)	NPH (once/twice daily)	-0.54	0.08	-0.54	0.09
RASKIN 2000[417]	Glargine (once daily)	NPH (once/twice daily)	-0.06	0.07	-0.11	0.07
RATNER 2000[420]	Glargine (once daily)	NPH (once/twice daily)	-0.16	0.05	-0.21	0.05
ROSENSTOCK 2000[437]	Glargine (once daily)	NPH (once/twice daily)	-0.40	0.05	-0.40	0.05
HOME 2005[222]	Glargine (once daily)	NPH (once/twice daily)	-0.21	0.05	-0.10	0.05
PIEBER 2000[408]	Glargine (once daily)	NPH (once/twice daily)	-0.25	0.05	-0.03	0.05
LE FLOCH 2009[281]	Detemir (once daily)	Detemir (twice daily)	-0.40	0.05	-0.50	0.05
RUSSELL JONES 2004[441]	Detemir (once daily)	NPH (once daily)	-0.06	0.04	0.06	0.07
GOLEN 2013[174]	Detemir (once daily)	NPH (once daily)	0.00	0.11	0.10	0.11
ZACHARIAH 2011[536]	NPH (once/twice daily)	Detemir (once/twice daily)	-0.70	0.26	-0.40	0.23
BARTLEY 2008[48]	NPH (once/twice daily)	Detemir (once/twice daily)	-0.72	0.08	-0.94	0.06

Abbreviations: SE, standard error

Table 65: Study data for severe/major hypoglycaemia

Study	Comparator 1	Comparator 2	Trial follow-up time (years)	Comparator 1		Comparator 2	
				N	NR	N	NR
CHATTERJEE 2007[84]	NPH (twice daily)	Glargine (once daily)	0.31	1	58	1	58
HERMANSEN 2004[206]	NPH (twice daily)	Detemir (twice daily)	0.35	45	297	40	298
HOME 2004[218]	NPH	Detemir	0.31	12	132	24	139

Study	Comparator 1	Comparator 2	Trial follow-up time (years)	Comparator 1		Comparator 2	
				N	NR	N	NR
	(twice daily)	(twice daily)					
STANDL 2004[473]	NPH (twice daily)	Detemir (twice daily)	1.00	20	135	35	154
VAGUE 2003[500]	NPH (twice daily)	Detemir (twice daily)	0.50	41	146	56	301
KOLENDORF 2006[263]	NPH (twice daily)	Detemir (twice daily)	0.31	33	128	19	125
PIEBER 2005[407]	NPH (twice daily)	Detemir (twice daily)	0.23	5	129	6	132
HELLER 2012[201]	Glargine (once daily)	Degludec (once daily)	1.00	23	157	90	472
MATHIEU 2013[310]	Glargine (once daily)	Degludec (once daily)	0.50	40	161	33	165
FULCHER 2005[156]	Glargine (once daily)	NPH (once daily)	0.58	131	63	119	65
RASKIN 2000[417]	Glargine (once daily)	NPH (once/twice daily)	0.31	29	310	20	309
RATNER 2000[420]	Glargine (once daily)	NPH (once/twice daily)	0.54	11	264	24	270
HELLER 2009[202]	Glargine (once daily)	Detemir (once/twice daily)	1.00	53	144	146	299
RUSSELL JONES 2004[441]	Detemir (once daily)	NPH (once daily)	0.50	68	491	32	256
HERMANSEN 2001[207]	NPH (once daily)	Detemir (once/twice daily)	0.12	11	56	4	57
BARTLEY 2008[48]	NPH (once/twice daily)	Detemir (once/twice daily)	2.00	237	164	148	331

Abbreviations: N, number of events; NR, number randomised

M.4.1 NMA results: Change in HbA1c

Both fixed effects and random effects models were fitted to the data. The random effects model had a better fit, with a DIC of -91.75 compared with -83.77 for the fixed effects model. The random effects model also has a total residual deviance of 49.62. This corresponds well to the total number of trial arms, 52. The between study variance in the random effects analysis was 0.008 (95% CrI: 0.028-0.001). Table 66 summarises the results of this analysis.

Table 66: Mean change in HbA1c from baseline

Insulin	Mean change*	Difference compared with NPH (twice daily)*	Lower 95% CrI	Upper 95% CrI
NPH (twice daily)	-0.320			
Glargine (once daily)	-0.423	-0.104	-0.335	0.138
Detemir (once daily)	-0.395	-0.076	-0.274	0.130
Detemir (twice daily)	-0.483	-0.164	-0.273	-0.048

Insulin	Mean change*	Difference compared with NPH (twice daily)*	Lower 95% CrI	Upper 95% CrI
NPH (four times daily	-0.008	0.310	0.022	0.622
Degludec (once daily)	-0.351	-0.032	-0.308	0.255
NPH (once daily)	-0.281	0.039	-0.248	0.332
NPH (once or twice daily)	-0.377	-0.057	-0.312	0.205
Detemir (once or twice daily)	-0.532	-0.212	-0.565	0.170

** Median of the posterior distribution for the mean change.*

Based on the direct comparisons (white area in Figure 257, below), efficacy, as assessed by reduction in HbA1c, favours insulin detemir (twice daily) over insulin NPH (twice daily). The other treatments compared with insulin NPH (twice daily) cross the line of no effect and no firm conclusion can be made.

Based on the results of the NMA (grey area in Figure 257), the evidence shows that insulin detemir (twice daily) is more effective than insulin NPH (twice daily) in reducing HbA1c. All other treatment comparisons in this network cross the line of no difference and statistical significance is not achieved.

No inconsistency was identified between the direct and NMA results for any comparison. All the differences from the NMA lie within the 95% confidence intervals from the direct comparison of the same treatments. It should be noted, however, that the direct comparison effect and NMA effect for insulin detemir (once daily) versus insulin glargine (once daily) have different directions of effect. Bucher's test was also used to assess inconsistency between the direct and idirect comparisons for the single loop in the network. The results showed that there is no significant inconsistency in the network (p=0.64).

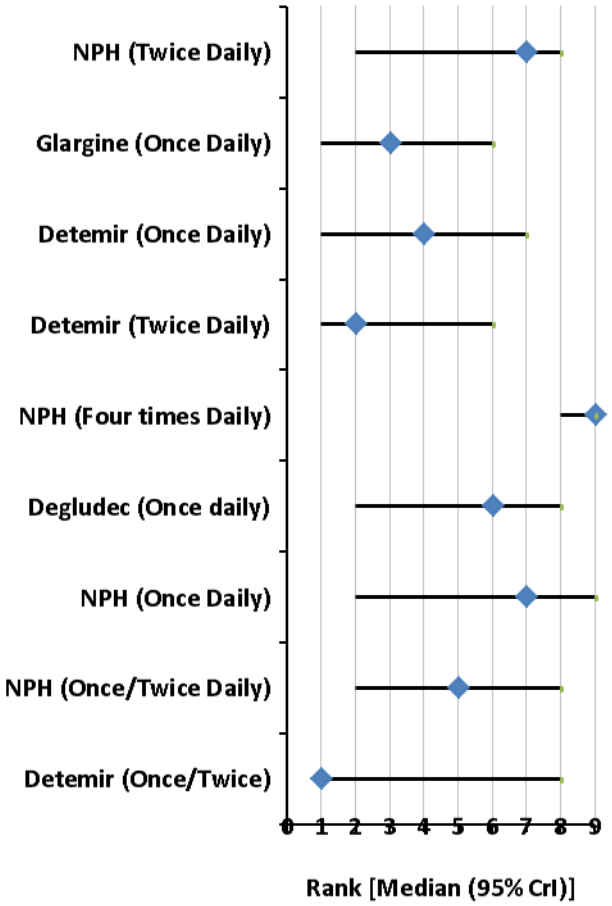
Figure 258 shows the rank of each intervention compared with all other treatments. The rank is based on the difference compared with insulin NPH (twice daily) and indicates the probability of being the best treatment, second best, third best and so on among the seven different interventions being evaluated. Insulin detemir (once or twice daily) is ranked first followed by Insulin detemir (twice daily), insulin glargine (once daily), insulin detemir (once daily), insulin NPH (once or twice daily), insulin degludec (once daily), insulin NPH (twice daily), insulin NPH (once daily) and insulin NPH (four times daily). The credible interval of the rank was wide for all treatments, spanning at least six ranks, except for NPH (four times daily) which could only be ranked either eighth or ninth.

Figure 257: Change in HbA1c, results of conventional and network meta-analyses

NPH (twice daily)	x	x	-0.15 (-030, 0.00)	x	x	x	x	x
-0.104 (-0.335,0.138)	Glargine (once daily)	-0.03 (-0.09,0.15)	-0.04 (-0.19,0.11)	0.40 (0.36,0.44)	0.07 (-0.02,0.17)		0.05 (-0.05,0.14)	x
-0.076 (-0.274,0.131)	0.028 (-0.155,0.208)	Detemir (once daily)	-0.09 (-0.19,0.00)	x	x	0.12 (-0.02,0.26)	x	x
-0.164 (-0.273,-0.049)	-0.061 (-0.269,0.146)	-0.089 (-0.256,0.08)	Detemir (twice daily)	x	x	x	x	x
0.310 (0.023,0.622)	0.414 (0.236,0.606)	0.386 (0.136,0.654)	0.475 (0.204,0.76)	NPH (four times daily)	x	x	x	x
-0.032 (-0.308,0.255)	0.072 (-0.08,0.224)	0.044 (-0.192,0.282)	0.132 (-0.124,0.391)	-0.343 (-0.586,-0.109)	Degludec (once daily)	x	x	x
0.039 (-0.248,0.333)	0.143 (-0.136,0.417)	0.115 (-0.095,0.323)	0.204 (-0.066,0.47)	-0.272 (-0.612,0.053)	0.071 (-0.248,0.384)	NPH (once daily)	x	x
-0.057 (-0.312,0.206)	0.047 (-0.06,0.151)	0.018 (-0.191,0.229)	0.108 (-0.127,0.34)	-0.368 (-0.587,-0.164)	-0.025 (-0.212,0.157)	-0.096 (-0.391,0.200)	NPH (once or twice daily)	-0.07 (-0.53,0.40)
-0.212 (-0.565,0.17)	-0.110 (-0.38,0.181)	-0.137 (-0.461,0.208)	-0.048 (-0.387,0.312)	-0.525 (-0.852,-0.184)	-0.181 (-0.491,0.147)	-0.251 (-0.634,0.154)	-0.155 (-0.41,0.114)	Detemir (once or twice daily)

Note: Results in the grey area are the medians of the posterior distribution of the difference in mean change and 95% credible intervals for the NMA of direct and indirect evidence between the row-defined treatment (intervention) versus the column-defined treatment (control). Results in the white area are the differences in mean change and 95% confidence intervals from the conventional meta-analyses of direct evidence between the column-defined treatment (intervention) versus the row-defined treatment (control).A negative value indicates reduction in HbA1c (favourable outcome).

Figure 258: Rank order for insulin regimens – reduction in HbA1c



M.4.2 NMA results: severe/major hypoglycaemia

Both fixed and random effects models were fitted to the data. The random effects model had a better fit, with a DIC of 225.73 compared to 257.81 for the fixed effects model. The random effects model has a total residual deviance of 31.3. This corresponds well to the total number of trial arms, 32. The between study variance from the random effects analysis was 0.317 (95% CrI: 0.093-1.266).

Table 67 presents the rate ratio for each intervention compared with insulin NPH (twice daily) from the NMA. The NMA also produced rate ratios for every possible pair-wise comparison, regardless of whether they have been compared in a clinical trial. These estimates are presented in Figure 259 alongside the rate ratios obtained from the direct MA pairwise comparisons.

Table 67: Rate of severe/major hypoglycaemic events

Insulin	Rate (events per person year)	Rate ratio compared with NPH (twice daily)	Rate ratio Lower 95% CrI	Rate ratio Upper 95% CrI
NPH (twice daily)	0.46			
Glargine (once daily)	0.47	1.33	0.02	101.20
Detemir (once daily)	0.61	0.96	0.54	1.74
Detemir (twice daily)	0.44	1.08	0.02	62.97
Degludec (once daily)	0.50	1.18	0.02	73.12
NPH (once daily)	0.54	1.63	0.03	94.43

Insulin	Rate (events per person year)	Rate ratio compared with NPH (twice daily)	Rate ratio Lower 95% CrI	Rate ratio Upper 95% CrI
NPH (once or twice daily)	0.75	0.63	0.01	36.24
Detemir (once or twice daily)	0.29	1.04	0.02	54.47

** Median of the posterior distribution for the mean change.*

Figure 259: Rate ratios for severe/major hypoglycaemia, results of conventional and network meta-analyses

NPH (twice daily)	1.00 (0.06, 15.99)	X	0.91 (0.69, 1.21)	X	X	X	X
1.04 (0.02,54.47)	Glargine (once daily)	X	X	1.03 (0.63, 1.67)	0.88 (0.69, 1.13)	1.18 (0.40, 3.54)	1.25 (0.92, 1.72)
1.33 (0.02,101.2)	1.26 (0.23,7.53)	Detemir (once daily)	X	X	0.90 (0.59, 1.37)	X	X
0.96 (0.54,1.74)	0.93 (0.02,43.99)	0.73(0.01,48.26)	Detemir (twice daily)	X	X	X	X
1.08 (0.02,62.97)	1.04 (0.4,2.72)	0.82 (0.11,5.69)	1.12 (0.02,68.03)	Degludec (once daily)	X	X	X
1.18 (0.02,73.12)	1.13 (0.4,3.54)	0.9 (0.23,3.45)	1.23 (0.02,79.64)	1.09 (0.27,4.9)	NPH (once daily)	X	0.36 (0.11, 1.12)
1.63 (0.03,94.43)	1.58 (0.65,3.67)	1.26 (0.18,7.7)	1.7 (0.03,101.9)	1.53 (0.41,5.41)	1.4 (0.35,4.82)	NPH (once or twice daily)	0.25 (0.20, 0.31)
0.63 (0.01,36.24)	0.61 (0.23,1.49)	0.48 (0.07,2.69)	0.65 (0.01,39.19)	0.58 (0.15,2.15)	0.53 (0.15,1.62)	0.38 (0.14,1.02)	Detemir (once or twice daily)

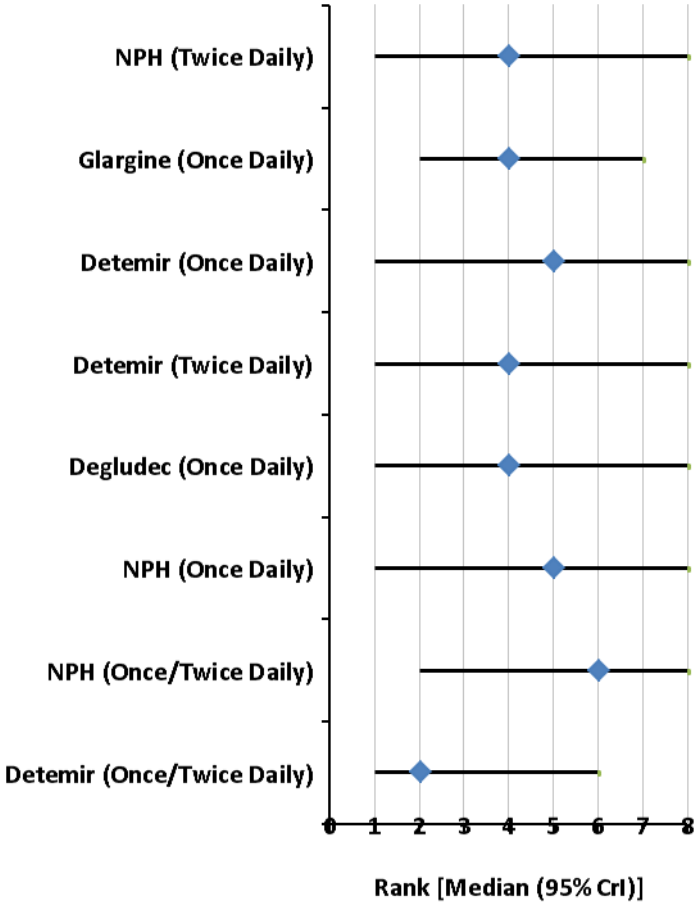
Note: Results in the grey area are the median rate ratios and 95% credible intervals for the NMA of direct and indirect evidence between the row-defined treatment compared with the column-defined treatment. Rate ratios of less than 1 favour the row-defined treatment. Results in the white area are the rate ratios and 95% confidence intervals from the conventional meta-analyses of direct evidence between the column-defined treatment compared with the row-defined treatment. Rate ratios of less than 1 favour the column-defined treatment.

Based on the direct comparisons (white area in Figure 259), efficacy, as assessed by the rate of severe/major hypoglycaemic events, neither insulin glargine (once daily) nor insulin detemir (once daily) is statistically significantly different from insulin NPH (twice daily).

Based on the results of the NMA (grey area in Figure 259), the evidence shows that none of the comparisons versus NPH (twice daily) has a treatment effect which reaches statistical significance. The rate ratios from the NMA lie within the 95% confidence interval from the direct comparison of the same treatments. Based on this, no inconsistency was identified between the direct and NMA results for any comparison. It should be noted, however, that the direct comparison effect and NMA effect for insulin NPH (once daily) versus insulin glargince (once daily) and insulin detemir (once or twice) versus insulin glargine (once daily) have different directions of effect. Additionally, the credible intervals around the treatment effect estimates are very wide, making it difficult to draw meaningful conclusions regarding the relative treatment effects on severe/major hypoglycaemia.

Figure 260 shows the rank of each intervention with respect to the rate of severe/major hypoglycaemia. As mentioned above, all interventions had very wide credible intervals around their rank, which made it difficult to fully characterise the order of efficacy. On the basis of the median rank, none of the insulin regimens is ranked first. Insulin detemir (once or twice daily) intervention is ranked second. Insulin detemir (twice daily), insulin glargine (once daily), insulin NPH (twice daily) and insulin degludec (once daily) have median rank of four followed by insulin NPH (once daily) and insulin detemir (once daily) both in rank five, then insulin NPH (once/twice).

Figure 260: Rank order for insulin regimens – severe/major hypoglycaemia



M.4.3 Summary of NMA results

In the ranking of the insulin regimens by change in HbA1c, insulin detemir (once or twice daily) was ranked first followed by insulin detemir (twice daily). Insulin NPH (four times daily), although a mean ranking of eight and was clearly the worst performing insulin regimen in relation to reducing HbA1c levels. Twice daily regimen of detemir ranked higher compared to the once daily regimen, however, for insulin NPH, both frequencies had similar median ranks but NPH (twice daily) had better median reduction of HbA1c compared to the once daily regimen.

In the ranking of insulin regimens by rate of severe/major hypoglycaemia, insulin detemir (once or twice daily) had the best median rank. The median rank of insulin detemir (twice daily), insulin glargine (once daily), insulin NPH (twice daily) and insulin degludec (once daily) was the same (4th), however, based on median treatment effect; insulin detemir (twice daily) came directly after insulin detemir (once or twice daily). All insulin regimens had very wide credible intervals, so; there is considerable uncertainty in the estimate of their rankings. Insulin NPH (once or twice daily) was ranked last. Similar to the results in relation to reduction in HbA1c, twice daily regimen of detemir ranked higher compared to the once daily regimen. The same was also seen for insulin NPH, where NPH (twice daily) had higher median rank compared to the once daily regimen. However, the credible intervals around these ranks are very wide and overlapping considerably.

M.5 Discussion

Based on the results of conventional meta-analyses of direct evidence, deciding upon the most effective long-acting basal insulin and insulin regimen for adults with type 1 diabetes is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, an NMA of all the available evidence was performed.

Our analyses were based on a total of 28 studies of nine different basal insulin regimens. The studies formed two networks of evidence each for a different outcome (change in HbA1c and number of severe/major hypoglycaemia). The findings from the NMA informed the original economic modelling undertaken to assess the cost effectiveness of these basal insulin regimens.

In the first network of change in HbA1c, insulin detemir (twice daily) was found to be more effective than insulin NPH (twice daily) (the network comparator) in reducing HbA1c. All other treatment comparisons in this network cross the line of no difference and statistical significance is not achieved. Insulin degludec (once daily) came sixth with high uncertainty as the credible interval was very wide and spanned six ranking positions. Insulin NPH (four times daily) was the worst performing and came in eighth rank with much less uncertainty and a credible interval that spanned only two ranking positions.

In the second network of severe/major hypoglycaemic events, none of the comparisons had a treatment effect which reaches statistical significance. However, it was likely that insulin detemir (once or twice daily) and insulin detemir (twice daily) are more effective than insulin NPH (twice daily) (the network comparator) but there is considerable uncertainty around these estimates. Insulin NPH (four times daily) was not included in this network.

The analysis compared all insulin regimens to insulin NPH (twice daily) and provides a hierarchy of insulin regimens. Contrary to a recently published NMA on this topic[495], the model chosen for the analysis of severe/major hypoglycaemic events presented here takes into account the fact that these are repeated events that can occur more than once for the same patient. The model also assumes that these events occur at a constant rate. Data presented in the trials show this is true after the first six to seven months of treatment. This model also provided treatment specifc estimates of event rates, which are inputted directly in the IMS CORE model used in the cost effectieveness analysis (see

Appendix N), as the model requires specifiying major hypoglycaemic event rates per 100 person years.

Our results are in line with that of Tricco et al.[495] in relation to the severe/major hypoglycaemia outcome, with insulin detemir (once or twice daily) is ranked first, while they were different in relation to the HbA1c outcome, where our analysis shows that insulin detemir (twice daily) achieved better reduction in HbA1c than insulin glargine (once daily). This reduction was also statistically significant compred to insulin NPH (twice daily). It has to be noted that the inclusion criteria, the model used for the analysis of severe/major hypoglycaemia and the long-acting insulin regimens in our NMA are different from Tricco et al.'s[495]. Our NMA also included trials of insulin degludec (once daily), which are not included in the Tricco et al. study[495].

The two outcomes chosen for this analysis are considered to be the most critical for assessing efficacy of long-acting basal insulin regimens. They are also used in the cost effectiveness analysis (see Appendix N). Weight gain is not included as an outcome in this analysis as the GDG did not consider it to be a critical outcome in type 1 diabetes patients.

M.6 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the reviews of long-acting insulin and insulin regimens even when direct comparative evidence was lacking.

Overall, the results of the two networks included in the main analysis showed that Insulin detemir (once or twice daily) appeared to be the long-acting insulin regimen that achieved best reduction in HbA1c and in the rate of severe/major hypoglycaemia. Of the seven regimens considered for de novo economic modelling, insulin detemir (twice daily) ranked the higest in terms of efficacy in relation to both outcomes.

M.7 WinBUGS Codes

M.7.1 HbA1c WinBUGS code- main NMA-Random Effects model

```
# Normal likelihood, identity link

# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:ns){                  #   LOOP THROUGH STUDIES

   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm

   delta[i,1] <- 0           # treatment effect is zero for control arm

   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines

   for (k in 1:na[i]) {           #  LOOP THROUGH ARMS

      var[i,k] <- pow(se[i,k],2)   # calculate variances

      prec[i,k] <- 1/var[i,k]      # set precisions

      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood

      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor

#Deviance contribution

      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]

    }

#  summed residual deviance contribution for this trial

   resdev[i] <- sum(dev[i,1:na[i]])

   for (k in 2:na[i]) {           # LOOP THROUGH ARMS

# trial-specific LOR distributions

      delta[i,k] ~ dnorm(md[i,k],taud[i,k])

# mean of LOR distributions, with multi-arm trial correction

      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]

# precision of LOR distributions (with multi-arm trial correction)

      taud[i,k] <- tau *2*(k-1)/k
```

```
# adjustment, multi-arm RCTs

       w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

       sw[i,k] <- sum(w[i,1:k-1])/(k-1)

     }

  }

# Ranking and prob[209]

 for (k in 1:nt) {

            rk[k]<-rank(d[],k)

best[k]<-equals(rank(d[],k),1)}

totresdev <- sum(resdev[])           #Total Residual Deviance

d[1]<-0      # treatment effect is zero for control arm

# vague priors for treatment effects

for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)     # vague prior for between-trial SD

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# Provide estimates of treatment effects T[k] on the natural scale

# Given a Mean Effect, meanA, for 'standard' treatment A,

# with precision (1/variance) precA

A ~ dnorm(meanA,precA)

for (k in 1:nt) { T[k] <- A + d[k]  }

for (c in 1:(nt-1))

{  for (k in (c+1):nt)

{  D[c,k] <- d[k] - d[c]}}

}                              # *** PROGRAM ENDS
```

Data

ns= number of studies; nt=number of treatments

list(ns=25,nt=9,meanA=-0.32, precA=132.93)

t[,1]	t[,2]	t[,3]	y[,1]	y[,2]	y[,3]	se[,1]	se[,2]	se[,3]	na[]
1	4	NA	-0.65	-0.82	NA	0.07	0.07	NA	2
1	4	NA	-0.30	-0.30	NA	0.06	0.06	NA	2
1	4	NA	-0.44	-0.65	NA	0.12	0.09	NA	2
1	4	NA	0.12	0.16	NA	0.10	0.09	NA	2
1	4	NA	-0.47	-0.58	NA	0.10	0.09	NA	2
1	4	NA	-0.18	-0.60	NA	0.05	0.05	NA	2
1	4	NA	-0.35	-0.48	NA	0.09	0.10	NA	2
2	3	NA	-0.19	-0.20	NA	0.05	0.09	NA	2
2	3	4	-0.54	-0.49	-0.58	0.06	0.05	0.05	3
2	6	6	-0.62	-0.57	-0.54	0.09	0.10	0.10	3
2	6	NA	-0.39	-0.40	NA	0.07	0.03	NA	2
2	6	NA	-0.58	-0.41	NA	0.06	0.06	NA	2
2	5	NA	-0.40	0.00	NA	0.01	0.02	NA	2
2	5	NA	-0.40	0.10	NA	0.17	0.10	NA	2
2	8	NA	-0.54	-0.54	NA	0.08	0.09	NA	2
2	8	NA	-0.06	-0.11	NA	0.07	0.07	NA	2
2	8	NA	-0.16	-0.21	NA	0.05	0.05	NA	2
2	8	NA	-0.40	-0.40	NA	0.05	0.05	NA	2
2	8	NA	-0.21	-0.10	NA	0.05	0.05	NA	2
2	8	NA	-0.25	-0.03	NA	0.05	0.05	NA	2
3	4	NA	-0.40	-0.50	NA	0.05	0.05	NA	2

3	7	NA	-0.06	0.06	NA	0.04	0.07	NA	2
3	7	NA	0.00	0.10	NA	0.11	0.11	NA	2
8	9	NA	-0.70	-0.40	NA	0.26	0.23	NA	2
8	9	NA	-0.72	-0.94	NA	0.08	0.06	NA	2

END

```
list(
d=c(NA,0,0,0,0,0,0,0,0),
sd=.2,
mu=c(-1,1,1,-1,3,1,0,0,1,-3,-1,0,-1,-3,3,3,-2,-3,-2,-2,3,-2,-2,3,-2))

list(
d=c(NA,0,0,0,0,0,0,0,0),
sd=.2,
mu=c(3,-1,-3,0,-3,-2,1,0,2,-1,0,2,-2,3,2,-3,1,-1,-3,2,-1,-3,-3,-1,-3))

list(
d=c(NA,0,0,0,0,0,0,0,0),
sd=.2,
mu=c(3,1,1,3,-3,-2,-2,-3,-1,0,-1,2,3,-1,3,0,3,-2,-2,-3,-2,1,1,-2,1))
```

M.7.2 Hypoglycaemia WinBUGS code-Main NMA- random Effects model

```
# Poisson likelihood, log link

# Random effects model for multi-arm trials

model{                          # *** PROGRAM STARTS

for(i in 1:ns){                 # LOOP THROUGH STUDIES

   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm

   delta[i,1] <- 0              # treatment effect is zero for control arm

   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines

   for (k in 1:na[i]) {           # LOOP THROUGH ARMS

      r[i,k] ~ dpois(theta[i,k])   # Poisson likelihood

      theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure

      log(lambda[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor

#Deviance contribution

      dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k]))          }

#  summed residual deviance contribution for this trial

   resdev[i] <- sum(dev[i,1:na[i]])

   for (k in 2:na[i]) {           # LOOP THROUGH ARMS

# trial-specific LOR distributions

      delta[i,k] ~ dnorm(md[i,k],taud[i,k])

# mean of LOR distributions (with multi-arm trial correction)
```

```
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]

# precision of LOR distributions (with multi-arm trial correction)

      taud[i,k] <- tau *2*(k-1)/k

# adjustment for multi-arm RCTs

      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials

      sw[i,k] <- sum(w[i,1:k-1])/(k-1)

    }
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

d[1]<-0      # treatment effect is zero for reference treatment

# vague priors for treatment effects

for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

sd ~ dunif(0,5)     # vague prior for between-trial SD

tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# Provide estimates of treatment effects T[k] on the natural (rate) scale

# Given a Mean Effect, meanA, for 'standard' treatment A,

# with precision (1/variance) precA

#A ~ dnorm(meanA,precA)

for (k in 1:nt) { log(T[k]) <- A + d[k]  }
```

```
# pairwise HRs and LHRs for all possible pair-wise comparisons, if nt>2

for (c in 1:(nt-1)) {

for (k in (c+1):nt) {

lhr[c,k] <- (d[k]-d[c])

log(hr[c,k]) <- lhr[c,k]

}
}
# ranking on relative scale

for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes events are "bad"

best[k] <- equals(rk[k],1) #calculate probability that treat k is best

}

}                              # *** PROGRAM ENDS


# A=log of rate for treatment 1


 Data
# ns= number of studies; nt=number of treatments

list(ns=16, nt=8, A=-0.7798)


r[,1]    r[,2]    t[,1]     t[,2]    na[]     E[,1]    E[,2]
1        1        1         2        2        18       18
45       40       1         4        2        103      103
12       24       1         4        2        41       43
```

20	35	1	4	2	83	146
41	56	1	4	2	29	50
33	19	1	4	2	39	38
5	6	1	4	2	30	30
23	90	2	5	2	144	429
40	33	2	5	2	81	83
131	119	2	6	2	36	38
29	20	2	7	2	95	95
11	24	2	7	2	142	145
53	146	2	8	2	133	292
68	32	3	6	2	246	128
11	4	6	8	2	6	7
237	148	7	8	2	296	740

END

#chain 1

list(d=c(NA, 0, 0, 0, 0, 0, 0, 0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0))

#chain 2

list(d=c(NA, -1, -3, -3, -3, -3, -3, -3), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3, -3))

#chain 3

list(d=c(NA, 2, -3, 5, -1, -3, 7, -3), sd=2, mu=c(-3, 5, -1, -3, 7, -3, -4, -3, -3, 0, -3, 5, -1, -3, 7, -3))

Appendix N: Cost-effectiveness analysis: Long-acting insulin and insulin regimen

N.1 Introduction

The GDG identified the comparison of long-acting insulins and insulin regimens, once or twice daily, as a high priority area for economic analysis. This was decided taking into account the considerable costs and health-related quality-of-life effects attributable to the long-term complications that arise from diabetes and unstable HbA1c control.

In 2002, NICE published Technology Appraisal (TA) 53 'Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine' which recommended insulin glargine as a treatment option for people with type 1 diabetes. [360] This guideline will update TA53.

The review questions linked to this high priority area are:

- In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?
- In adults with type 1 diabetes, is once daily basal insulin more effective than twice daily basal insulin for optimal diabetic control?

Direct meta-analysis and network meta-analysis (NMA) were undertaken as part of the clinical review. The results of these meta-analyses are reported in the full guideline (Chapter 10).

In the economic literature review, ten economic evaluations were included that addressed the first question.[73,183,322,390,392,401,497,502,504,514] Details of these studies are included in Chapter 10 of the full guideline. Five cost-utility analyses found that insulin detemir was cost effective compared to NPH (ICERs: £2,500, £3,443, £9,526, £12,989 and £19,285 per QALY gained).[390,392,497,502,505] Another cost-utility analysis found that insulin detemir was not cost effective compared to NPH (ICER: £206,488 per QALY gained).[73] Three cost-utility analyses found that insulin glargine was cost effective compared to NPH (ICERs: £3,496 - £4,978, £3,189 - £9,767 and £10,903 per QALY gained),[183,322,514] one study found that insulin glargine was dominant compared to NPH,[401] while another found that insulin glargine was not cost effective compared to NPH (ICER: £46,829 per QALY gained).[73] One cost-utility analysis found that insulin detemir was dominant (less costly and more effective) over insulin glargine, [505] while another found that glargine was the dominant option when compared to detemir.[73] The review did not identify any economic evaluations that addressed the second review question, comparing once with twice daily long-acting insulin regimens. Given the importance of these questions in terms of both costs and health benefits, the uncertainty and the poor quality of the available evidence, an original economic analysis was deemed necessary.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- The GDG was consulted during the construction and interpretation of the model.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

N.2 Methods

N.2.1 Model overview

A previously published diabetes model that has been validated against clinical and epidemiological data was used for the analysis (IMS CORE Diabetes Model (CDM)). This was decided given the complexity of modelling type 1 diabetes as a disease with many complications and the limited time available during this clinical guideline development .Hence, the decision was taken across NICE diabetes guidelines, which are being simultaneously developed, to use this widely used and validated model.

The IMS CDM is an internet-based, interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. The type 1 diabetes data were selected for running our analysis.

Insulin regimens that reduce and improve the stability of HbA1c are likely to reduce short-term complications such as hypo- and hyperglycaemia and also reduce the occurrence of long-term complications. As such, economic modelling was undertaken to determine the most cost effective basal insulin regimen. The analysis is based on the benefits of lowering HbA1c and reducing severe hypoglycaemia.

N.2.1.1 Comparators

The following strategies were compared against each other:

- Detemir once daily
- Detemir twice daily
- Glargine once daily
- Degludec once daily
- NPH once daily
- NPH twice daily
- NPH four times daily

The daily dose was assumed to be the same for all comparators (24 units), which is the average daily dose based on the GDG opinion. This dose would be given in divided doses for comparators with higher dosing frequency (twice or four times daily).

N.2.1.2 Population

The base case (primary analysis) considered a cohort of adults representing the average individuals with type 1 diabetes in the UK. In a sensitivity analysis, data representing a population with a more recent diagnosis oftype 1 diabetes in the UK were selected.

N.2.1.3 Time horizon, perspective, discount rates used

A time horizon of 80 years was used in the base case as this was deemed sufficient to consider lifetime costs and outcomes (note that in the CORE model the number of years has to be specified to define the time horizon). Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.[365] A sensitivity analysis using a discount rate of 1.5% for both costs and health benefits was conducted.

N.2.2 Approach to modelling

N.2.2.1 Model structure

The CORE Diabetes Model is a validated, non-product specific diabetes policy analysis tool that allows performing simulations taking into account the use of intensive or conventional insulin therapy, oral hypoglycaemic medications, screening and treatment strategies for microvascular complications, treatment strategy for end stage complications and multifactorial interventions.

It simulates diabetes progression using a series of interlinked, inter-dependent sub-models which simulate the following diabetes complications:

- angina,
- myocardial infarction,
- congestive heart failure,
- stroke,
- peripheral vascular disease,
- diabetic retinopathy,
- macular oedema,
- cataract,
- hypoglycaemia,
- ketoacidosis,
- lactic acidosis,
- nephropathy and end-stage renal disease,
- neuropathy,
- foot ulcer,
- amputation
- and non-specific mortality.

Each of these sub-models is a Markov model which uses time-, state- and diabetes type-dependent probabilities that have been derived from published sources. Interaction between the individual complication sub-models is mediated through the use of Monte Carlo simulation using tracker variables.[389]

The model has been validated extensively against epidemiological and clinical studies of type 1 diabetes.[321] Full description of the CORE model and its modules and sub-models is given in Palmer et al (2004).[389]

N.2.2.2 Uncertainty

The CORE model could also be run probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly (1000 times) for the base case and results were summarised. Distributions around different parameters are set by default in the CORE model and these are explained in the document available on the CORE website.[227]

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),

- long-acting insulin treatment costs

In addition, other sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

N.2.2.3 Summary table of model inputs

The CORE model input parameters are grouped under the following input databases:

a. cohort
b. economics
c. other management
d. clinical
e. treatment
    i. clinical effectiveness
    ii. costs

Parameters for all the databases except for the treatment database were common in all the three analyses developed for this guideline and are reported below. Treatment specific data (costs and effectiveness) are reported in separate paragraphs and differ between analyses.

The default model inputs for type 1 diabetes were validated with the clinical members of the GDG and, if found appropriate, were used. Where more reliable or recent UK sources were identified, these were used instead. **Error! Reference source not found.** to **Error! Reference source not found.** ist the input parameters that were updated in each of the model modules and their sources.

More details about sources, calculations and rationale for selection can be found in the sections following these summary tables.

a) Cohort parameters

In the CORE model the initial population cohort is defined in terms of age, gender, baseline risk factors and pre-existing complications. The model default cohort characteristics were updated to reflect a UK-based, adult, type 1 diabetes population. Baseline complications were assumed nil unless reliable UK data could be identified (for example for stroke and angina). The cohort parameters used in the three analyses performed in this guideline and their sources are outlined in **Error! Reference source not found.**.

Table 68: Baseline cohort characteristics

Input variable	Mean	SE/SD	Source/comment
Patient demographics			
Start age (years)	42.98	19.14	DCCT, [353] n= 1441
Duration of Diabetes (years)[(a)]	16.92	13.31	National Diabetes Audit[18]
Proportion Male [(a)]	56.7%		National Diabetes Audit[18]
Baseline risk factors			
HbA1c (%-points) [(a)]	8.6	4.0	National Diabetes Audit[18]
Systolic Blood Pressure (%-points) [(a)]	128.27	16.07	National Diabetes Audit[18]
Total cholesterol (mg/dL)	176.50	33	DCCT[353]

Input variable	Mean	SE/SD	Source/comment
HDL (mg/dL)	50.25	13	DCCT[353]
LDL (mg/dL)	109.75	29	DCCT[353]
Triglycerides (mg/dL)	81.50	41	DCCT[353]
Body mass index (BMI) kg/m2[(a)]	27.09	5.77	National Diabetes Audit[18]
Proportion smoker[(a)]	0.22		National Diabetes Audit[18]
Cigarettes/day	12		Opinions and Lifestyle Survey, Smoking Habits Amongst Adults, 2012[379]
Alcohol consumption (oz/week)	9		[13.37 litres per year] UK data from WHO Global Status Report on Alcohol 2011. Geneva: WHO 2011[528]
eGFR (ml/min/1.73m^2)	77.5	0	Default in CORE model
Haemoglobin (gr/dl)	14.5	0	Default in CORE model
White blood cells (10^6/ml)	6.8	0	Default in CORE model
Heart rate (bpm)	72	0	Default in CORE model
Racial characteristics			
Proportion White/Mixed/Other[(a)]	0.92		National Diabetes Audit[18]
Proportion Black[(a)]	0.03		National Diabetes Audit[18]
Proportion Asian[(a)]	0.05		National Diabetes Audit[18]
Baseline CVD complications			
Proportion with myocardial infarction (MI)	0.000		Assumed nil
Proportion with angina	0.00298		England Health Survey 2011 - Angina in 25 - 34 age group[199]
Proportion with peripheral vascular disease (PVD)	0.000		Assumed nil
Proportion with stroke	0.00298		England Health Survey 2011 - stroke in 25 - 34 age group[199]
Proportion with heart failure	0.000		Assumed nil
Proportion with atrial fibrillation	0.000		Assumed nil
Proportion with Left Ventricular Hypertrophy (LVH)	0.000		Assumed nil
Baseline renal complications			
Proportion with micro-albuminuria[(a)]	0.181		National Diabetes Audit[18]
Proportion with gross-proteinuria	0.000		Assumed nil
Proportion with end-stage renal disease	0.000		Assumed nil
Baseline eye disease complications			

Input variable	Mean	SE/SD	Source/comment
Proportion with background diabetic retinopathy	0.000		Assumed nil
Proportion with proliferative diabetic retinopathy	0.000		Assumed nil
Proportion with severe vision loss	0.000		Assumed nil
Proportion with macular oedema	0.000		Assumed nil
Proportion with cataract	0.000		Assumed nil
Baseline foot ulcer complications			
Proportion with uninfected ulcer	0.000		Assumed nil
Proportion with infected ulcer	0.000		Assumed nil
Proportion with healed ulcer	0.000		Assumed nil
Proportion with history of amputation	0.000		Assumed nil
Baseline neuropathy			
Proportion with neuropathy	0.049		DCCT [353]
Baseline depression			
Proportion with depression	0.210		Hopkins et al (2012)[223]

(a) This publication is based on data collected by or on behalf of the Healthcare Quality Improvement Partnership, who have no responsibility or liability for the accuracy, currency, reliability and/or correctness of this publication.

b) Economics

The economics database contains costs of managing chronic and recurrent conditions and costs of complications (**Error! Reference source not found.**), together with quality of life (QoL) data (**Error! eference source not found.**). We updated the default values in the CORE model to reflect the UK costs and clinical practice. Indirect costs were not included in our analysis and these parameters in the CORE model were set to 0.

All costs from sources published before 2013 were inflated to 2013 using the 2012/13 HCHS index available in PSSRU 2013.[107] In the source/comments column we report the original uninflated value. Where IMS default values were used this has been clarified in the source/comment column.

Table 69: Economic database - management and complications costs

Input variable	Mean cost per year (£)	Source/comment
Management costs		
Statins	38.22	Atorvastatin 80mg 28 days. NHS Drug Tariff 2014[369]
Aspirin	10.40	Following ischemic event; 75mg 28 days. NHS Drug Tariff 2014[369] - [default in CORE model]

ACE-inhibitors	18.54	Average cost of 5 generics. NHS Drug Tariff 2014[369]
Screening for micro-albuminuria	3.02	Weighted: 80% once per year; 20% three times per year; unit cost £2.16[276]
Screening for gross proteinuria	2.91	2 per year; unit cost £1.42[276] inflated to 2013 costs
Stopping ACE-inhibitors due to side effects	19.96	28 days of Angiotensin receptor antagonist (losartan 50mg or candesartan 8mg). NHS Drug Tariff 2014[369]
Eye screening	35	Based on annual national cost of £70m for 2 million diabetics screen once per year (based on personal communication with UK National Screening Committee, Dec 2013)
Foot screening program	42	Podiatrist outpatient visit, NHS reference cost 2012/13[122]
Non-standard ulcer treatment (for example, Regranex)	0	Default in CORE model (Regranex has been discontinued in the UK)
Anti-depression treatment and management	489	See **Error! Reference source not found.**
Screening for depression	0	Part of standard management
Annual costs CVD complications (repeated every year)		
MI first year	3,731	NICE Lipids guideline, CG181[355] For the cost of angina it was assumed that one third of angina episodes would be unstable and two thirds would be stable.
MI second plus years	788	
Angina first year	6,406	
Angina second plus years	288	
Chronic heart failure first year	3,596	
Chronic heart failure second plus years	2,597	
Stroke first year	4,170	
Stroke second plus years	155	
Stroke death within 30 days	1,174	
Peripheral vascular disease first year	952	
Peripheral vascular disease second plus years	529	
Annual costs renal complications (repeated every year)		
Haemodialysis	30,480	NICE Peritoneal Dialysis clinical guideline, CG125.[364] Costs inflated to 2012/13.[107]
Peritoneal dialysis	24,520	
Renal transplant first year	20,373	
Renal transplant second plus years	7,609	
Costs of acute events (event-based)		
Major hypoglycaemic events	434	See **Error! Reference source not found.**
Minor hypoglycaemic events	0	GDG assumption that all would be dealt with at home
Ketoacidosis events	0	This parameter was not used in the model as no data were available on ketoacidosis event rates associated with the interventions compared in the economic analyses.
Lactic acid events	0	Assumed no cost of management required (expert opinion)
Oedema onset	0	Assumed no cost of management required (expert opinion)

Oedema follow up	0	Assumed no cost of management required (expert opinion)
Costs of eye disease		
Laser treatment	697	NHS reference cost 2012/13[122]: BZ24D Non-surgical ophthalmology with interventions
Cataract operation	1,024	Weighted NHS reference cost 2012/13[122]: Non-phacoemulsification cataract surgery, with Complication score 0 (BZ03A) and score 1+ (BZ03B)
Following cataract operation	80	NHS reference cost 2012/13[122]: WF01A: Non-admitted face to face attendance, ophthalmology follow-up
Blindness - year of onset	5,585	NICE Glaucoma clinical guideline, CG85[357]
Blindness - following years	5,396	
Costs neuropathy/foot ulcer/amputation		
Neuropathy first year	361.60	MIMS April 2014 (online version), Duloxetine 60 mg daily (first-line treatment in CG96) – [default in CORE model]
Neuropathy second plus years	361.60	
Amputation (event based, not annual cost)	11,290	NICE Lower limb peripheral arterial disease (PAD) clinical guideline (CG147)[354]
Amputation with Prosthesis (event based)	15,250	NICE Lower limb peripheral arterial disease (PAD) clinical guideline (CG147)[354]
Gangrene treatment	3,008	Ghatnekar et al (2002)[164] – inflated to 2014[default in CORE model]
Cost after healed ulcer	5,483	
Infected ulcer	7,328	Insight Health Economics 2012[228,354]
Standard uninfected ulcer	4,070	
Healed ulcer history of amputation	25,295.71	NICE Lower limb peripheral arterial disease (PAD) clinical guideline (CG147)[354]

Cost of depression

In order to estimate the annual cost of depression management, the following resources were considered:

a. Drug treatment
b. Group physical activity
c. Peer support
d. CBT
e. Collaborative care
f. Relapses

Details of calculations are reported in **Error! Reference source not found.**.

Table 70: Cost of depression management

Item	Proportion of patients receiving care	Annual cost	Weighted annual cost	Details/Source of cost
Drug treatment	50%	£39.40	£19.70	Weighted average of cost of all antidepressant preparations available in the UK[94]
Group physical activity	15%	£249	£37.29	Resource use from CG91 - Depression in adults with a chronic

Item	Proportion of patients receiving care	Annual cost	Weighted annual cost	Details/Source of cost
				physical health problem.[356] Counselling services in primary medical care - Cost per consultation is £58[107] 2.5 sessions per week for a course of 10-14 weeks (12 on average): £58*2.5*12=£1,740. The session is delivered to 6-8 people at a time (average 7): £1,740/7 = £249
Peer support	15%	£82.86	£12.43	Resource use from CG91 - Depression in adults with a chronic physical health problem.[356] Counselling services in primary medical care - Cost per consultation is £58[107] 1 session per week for a course of 8-12 weeks (10 on average): £58*1*10=£580. The session is delivered to 6-8 people at a time (average 7): £580/7 = £82.86
Cognitive-behavioural Therapy	10%	£406	£40.60	Resource use from CG91 - Depression in adults with a chronic physical health problem.[356] Counselling services in primary medical care - Cost per consultation is £58[107] 6-8 sessions (average 7) over 9-12 weeks: £58*7=£406.
Collaborative care	10%	£1,287	£128.73	CG91 - Depression in adults with a chronic physical health problem.[356] Cost uplifted to 12/13 prices using Hospital and Community Price and Pay Index 2012/13[107]
Relapse	34%	£737.43	£250.73	Sum of cost of group physical activity, peer support, and CBT.

Cost of major hypo events

The cost of major hypoglycaemic events was calculated based on the NHS reference costs 2012/13[122] as the source of unit costs and Farmer et al (2012)[146] and Leese et al. (2003)[286] as the sources of resource use estimates. Details of the calculation are reported in **Error! Reference source not found.** elow.

Table 71: Cost of hypoglycaemic events

Item	Proportion of patients receiving care [(a)]	Unit cost [(b)]	Weighted cost
Dealt with at home by family member	7%	£0	£0
Ambulance only	34%	£173	£59
A & E (or primary care) only - A&E not admitted - VB08Z	7%	£134	£9
Ambulance and A&E	14.56%	£1,532	£223

Item	Proportion of patients receiving care [(a)]	Unit cost [(b)]	Weighted cost
admitted (VB08Z), and hospital stay KB01A/KB02A			
Ambulance and A&E not admitted - VB08Z	37.44%	£361	£135
Total			***£426***

(a) Farmer et al (2012)[146] and Leese et al. (2003)[286]
(b) NHS Reference Costs 2012/13[122]

Quality of life parameters

All the quality of life parameters in the model were the default values of the CORE model, with the exception of the value associated with major hypoglycaemic events (**Error! Reference source not ound.**). The quality of life value associated with a major hypoglycaemic event was derived by the study by Currie et al (2006)[104] where the Hypo Fear Survey results of 5.881 was then multiplied by the conversion factor (-0.008) to give a utility decrement of -0.047 for anyone experiencing an event. As the survey is based on 3-month data, the utility decrement has been divided by 4 to obtain the annual utility decrement for anyone experiencing a severe hypo in a year (-0.012). This adjustment has been accepted by previous publications and TA submissions.

In the base case analysis the minimum approach was selected, whereby if an individual in the model has more than one condition, the quality of life of the condition which has the lowest value is applied and the other conditions ignored as their impact on quality of life is negligible. This was changed in a sensitivity analysis where the multiplicative approach was selected and the quality of life values of concurrent conditions are multiplied to derive an overall utility score. Some events are associated with disutilities that are applied for one year to the health state utility as defined by the minimum approach.

Table 72: Economic database - quality of life values

Input variable	Mean	Source/comment
QoL no complications	0.814	UKPDS6[90]
QoL loss - MI event	-0.055	Beaudet et al (2014)[49]
QoL post MI	0.759	Assumed equal to baseline utility minus MI event
QoL angina	0.695	Beaudet et al (2014)[49]
QoL chronic heart failure	0.677	
QoL loss - stroke event	-0.164	
QoL post stroke	0.650	Assumed equal to baseline utility minus stroke event
QoL peripheral vascular disease	0.7240	Beaudet et al (2014)[49]
QoL micro-albuminuria	0.814	Assumed equal to baseline
QoL gross-proteinuria	0.7370	Beaudet et al (2014)[49]
QoL haemodialysis	0.6210	
QoL peritoneal disease	0.5810	
QoL renal transplant	0.7620	
QoL background diabetic retinopathy	0.7450	
QoL background diabetic retinopathy wrongly treated	0.7450	

Input variable	Mean	Source/comment
QoL proliferative diabetic retinopathy laser treated	0.7150	
QoL proliferative diabetic retinopathy no Laser	0.7150	
QoL macular oedema	0.7450	
QoL severe visual loss	0.7110	
QoL cataract	0.7690	
QoL neuropathy	0.7010	
QoL healed ulcer	0.814	Assumed equal to baseline
QoL active ulcer	0.6150	Beaudet et al (2014)[49]
QoL loss - amputation event	-0.2800	
QoL post amputation	0.534	Assumed equal to baseline utility minus amputation event
QoL loss - major hypo events	-0.012	Currie et al (2006)[104]
QoL loss - minor hypo events	0.00	Assumed no loss of utility
QoL fear of hypo event	0.0000	Included in the disutility for the hypo event itself
QoL loss - keto event	0.0000	Assumed no loss of utility
QoL loss - lactic acid event	0.0000	Assumed no loss of utility
QoL loss - oedema event	-0.040	Matza et al(2007)[311]
QoL post oedema	0.8140	Assumed equal to baseline
QoL depression not treated	0.6059	Goldney et al (2004)[173] [Conversion of SF-36 scores to SF-6D values]
QoL depression treated	0.8140	Assumed equal to baseline

There was some uncertainty around the disutility value of a major hypoglycaemic event as this was measured in a population with both type 1 and type 2 diabetes, therefore this value was subject to sensitivity analysis. The disutility of a minor hypoglycaemic event was uncertain as well but this outcome was not reported for any of the comparisons in our analyses therefore it was not necessary to explore the uncertainty.

c) Other management

Where possible the default CORE values were substituted with UK-specific data, otherwise the default values were kept in the analysis.

Table 73: Database inputs - management parameters

Input variable	Mean	Source/comment
Concomitant medications		
Proportion on aspirin for primary prevention	46%	Minshall et al (2008)[333] [default in CORE model]
Proportion on aspirin for secondary prevention	76%	Gerstein et al (2008)[163] [default in CORE model]
Proportion on statins for primary prevention	45%	Minshall et al (2008)[333] [default in CORE model]
Proportion on statins for secondary prevention	88%	Gerstein et al (2008)[163] [default in CORE model]

Input variable	Mean	Source/comment
Proportion on ACE-inhibitors for primary prevention	50%	Minshall et al (2008)[333] [default in CORE model]
Proportion on ACE-inhibitors for secondary prevention	71%	Gerstein et al (2008)[163] [default in CORE model]
Screening and patient management proportions		
Proportion on foot ulcer prevention program[(a)]	99%	National Diabetes Audit[18]
Proportion screened for eye disease	100%	No UK data; assumed to be included in standard management.
Proportion screened for renal disease	100%	No UK data; assumed to be included in standard management.
Proportion receiving intensive insulin after MI	88%	McMullin et al (2004)[324] [default in CORE model]
Proportion treated with extra ulcer treatment	57%	Lyon (2008)[300] [default in CORE model]
Proportion screened for depression - no complications	83%	Jones et al (2007)[239] [default in CORE model]
Proportion screened for depression - complications	83%	
Others		
Reduction in incidence of foot ulcers with Prevention Programme	31%	O'Meara et al (2000)[378] [default in CORE model]
Improvement in ulcer healing rate with extra ulcer treatment (multiplier)	1.390	Kantor et al (2001)[241] [default in CORE model]
Reduction in amputation rate with footcare	34%	O'Meara et al (2000)[378] [default in CORE model]
Sensitivity of eye screening	92%	Lopez-Bastida et al (2007)[297] [default in CORE model]
Specificity of eye screening	96%	
Sensitivity of gross proteinuria screening	83%	Cortes et al (2006)[97] [default in CORE model]
Sensitivity of low-level (micro) albuminuria screening	83%	
Specificity of low-level (micro) albuminuria screening	96%	

(a) This publication is based on data collected by or on behalf of the Healthcare Quality Improvement Partnership, who have no responsibility or liability for the accuracy, currency, reliability and/or correctness of this publication.

d) Clinical

This module contains data that describe the natural history of the disease and uses probabilities and relations between diabetes type-specific risk factors, where data allow this. In our analyses we used the default values in the CORE model for type 1 diabetes.

Table 74: Clinical database - clinical parameters

Input variable	Mean	Source/comment
HbA1c adjustments		
Reduction in risk of background diabetic retinopathy with 10% lower HbA1c	39%	DCCT[6]
Reduction in risk of proliferative diabetic retinopathy with 10% lower HbA1c	43%	
Reduction in risk of severe vision loss with 10% lower HbA1c	0%	No data
Reduction in risk of macular oedema with 10% lower HbA1c	13%	Klein et al (2009)[259]
Reduction in risk of micro-albuminuria with 10% lower HbA1c	28%	DCCT[6]
Reduction in risk of gross-proteinuria with 10% lower HbA1c	37%	
Reduction in risk of end stage renal disease with 10% lower HbA1c	21%	Rosolowsky et al (2011)[438]
Reduction in risk of neuropathy with 10% lower HbA1c	32%	DCCT[6]
Reduction in risk of MI with 1% lower HbA1c	20%	
Reduction in risk of cataract with 1% lower HbA1c	0%	Grauslund et al (2011)[180]
Reduction in risk of heart failure with 1% lower HbA1c	23%	Lind et al (2011)[294]
Reduction in risk of stroke with 1% lower HbA1c	20%	DCCT[6]
Reduction in risk of angina with 1% lower HbA1c	20%	
Reduction in risk of haemodialysis mortality with 1% lower HbA1c	12%	Morioka et al (2001)[343]

Reduction in risk of peritoneal dialysis mortality with 1% lower HbA1c	12%	
Reduction in risk of renal transplant mortality with 1% lower HbA1c	0%	Wiesbauer et al (2010)[523]
Reduction in risk of 1st ulcer with 1% lower HbA1c	17%	Monami et al (2009)[336]
Systolic BP adjustments		
Reduction in risk of micro-albuminuria with 10mmHG lower SBP	13%	Adler et al (2000)[22]
Reduction in risk of severe visual loss with 10mmHG lower SBP	0%	No data
Myocardial infarction adjustments		
Proportion with MI having an initial coronary heart disease (CHD) event, Female	0.361	D'Agostino et al (2000)[108]
Proportion with MI having an initial CHD event, Male	0.522	
Proportion with MI having an subsequent CHD event, Female	0.474	
Proportion with MI having an subsequent CHD event, Male	0.451	
RR MI if micro-albuminuria is present	1.00	No data
RR MI if gross-proteinuria is present	1.00	
RR MI if end stage renal disease is present	1.00	
RR recurrent MI if DIGAMI intensive control is used	1.00	
RR MI mortality if DIGAMI intensive control is used	1.00	
RR MI if on aspirin for primary prevention	0.82	Baigent et al (2009)[45]
RR MI if on aspirin for secondary prevention	0.80	
RR MI if on statin for primary prevention	0.70	Brugts et al (2009)[69]
RR MI if on statin for secondary prevention	0.81	Shepherd et al (2002)[458]

RR MI if on ACE-inhibitors for primary prevention	0.78	HOPE Study Investigators (2000)[9]
RR MI if on ACE-inhibitors for secondary prevention	0.78	D'Agostino et al (2000)[108]
Myocardial infarction mortality		
Probability sudden death after 1st MI, male	39%	Sonke et al (1996)[469]
Probability sudden death after 1st MI, female	36%	
Probability sudden death after recurrent MI, male	39%	
Probability sudden death after recurrent MI, female	36%	
RR 12 month mortality after MI	1.45	Malmberg et al (1995)[303]
RR mortality if use of aspirin, 1st year after MI	0.88	Antiplatelet Trialists' Collaboration 1994[3]
RR mortality if use of aspirin, 2nd year and more after MI	0.88	
RR mortality if use of statin, 1st year after MI	0.75	Stenestrand et (2001)[477]
RR mortality if use of statin, 2nd year and more after MI	1.00	No data
RR sudden death if use aspirin, after MI	1.00	No data
RR sudden death if use statin, after MI	1.00	Briel et al (2006)[66]
RR sudden death if use ACE-inhibitor, after MI	1.00	No data
RR long term mortality following MI using ACE-inhibitor	0.64	Gustafsson et al (1999)[190]
RR 12 month mortality following MI using ACE-inhibitor	0.64	Sonke et al (1996)[469]
Stroke adjustments		
RR stroke with micro-albuminuria	1.00	No data
RR stroke with gross-proteinuria	1.00	
RR stroke with end stage renal disease	1.00	
RR 1st stroke if on aspirin	0.86	Baigent et al (2009)[45]

RR 2nd stroke if on aspirin	0.78	
RR 1st stroke if on statins	0.81	Brugts et al (2009)[69]
RR 2nd stroke if on statins	0.84	The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators (2006)[31]
RR 1st stroke if on ACE-inhibitors	0.67	HOPE Study Investigators (2000)[9]
RR recurrent stroke if on ACE-inhibitors	0.72	PROGRESS Collaborative Group (2001)[11]
Stroke mortality		
30-day probability of death after 1st stroke	0.124	Eriksson et al (2001)[141]
30-day probability of death recurrent stroke	0.422	
RR stroke mortality if on aspirin	0.84	Antiplatelet Trialists' Collaboration 1994[3]
RR stroke mortality if on statins	1.00	Manktelow et al (2009)[304]
RR sudden death after stroke if on aspirin	0.95	Sandercock et al (2008)[445]
RR sudden death after stroke if on statins	1.00	Briel et al (2006)[66]
RR sudden death after stroke if on ACE-inhibitors	0.49	Chitravas et al (2007)[89]
RR long-term mortality after stroke if on ACE-inhibitors	1.000	Asberg et al (2010)[41]
RR 12 month mortality after stroke if on ACE-inhibitors	1.000	Eriksson et al (2001)[141]
Angina		
Proportion initial CHD event angina, Female	0.621	D'Agostino et al (2000)[108]
Proportion initial CHD event angina, Male	0.420	
Proportion subsequent CHD event angina, Female	0.359	
Proportion subsequent CHD event angina, Male	0.301	
RR angina with micro-albuminuria	1.00	No data
RR angina with gross-proteinuria	1.00	No data
RR angina with end stage renal disease	1.00	No data
Congestive heart failure		

RR HF if micro-albuminuria	1.00	No data
RR if gross-proteinuria	1.00	No data
RR HF if end stage renal disease	1.00	No data
RR HF if using aspirin	1.00	No data
RR HF if using statin	1.00	No data
RR HF if using ACE-inhibitors	0.80	HOPE Study Investigators (2000)[9]
RR HF death if using ACE-inhibitors	0.80	Ascencao et al (2008)[42]
RR HF death in diabetic male	1.00	Ho et al (1993)[214]
RR HF death diabetic female	1.70	
ACE inhibitor adjustments for micro-vascular complications		
RR background diabetic retinopathy using ACE-inhibitors	0.75	Chaturvedi et al (1998) [85]
RR proliferative diabetic retinopathy using ACE-inhibitors	0.19	
RR macular oedema using ACE-inhibitors	1.00	No data
RR severe visual loss using ACE-inhibitors	1.00	
RR worsening micro-albuminuria with ACE-inhibitors, no complication	0.79	Penno et al (1998)[396]
RR worsening gross-proteinuria with ACE-inhibitors, if micro-albuminuria is present	0.41	
RR worsening end stage renal disease with ACE-inhibitors, if gross-proteinuria	0.63	Lewis et al (1993) [292]
RR neuropathy with ACE-inhibitors	1.00	No data
ACE-inhibitors side effects		
Probability side effects stopping ACE-inhibitors	0%	Assumed nil
Adjustments for race		
Background diabetic retinopathy, proliferative diabetic retinopathy, severe visual loss, neuropathy		No adjustment made
Adverse events		

Probability of death from major hypo event	0%	Assumed nil
Probability of death from ketoacidosis event	3%	MacIsaac et al (2002)[301]
Probability of death from lactic acidosis event	43%	Campbell et al (1985)[74]
RR hypo events with ACE-inhibitors	1.00	No data
Foot ulcer and amputation		
Probability gangrene to amputation	18%	Persson et al (2000)[398]
Probability gangrene to healed amputation	31%	
Probability of death following onset gangrene	1%	
Probability of death if history amputation is present	0%	
Probability of death following healed ulcer	0%	
Probability of developing recurrent uninfected ulcer	4%	
Probability of amputation following infected ulcer	0%	
Probability of infected ulcer after amputation healed	4%	
Probability of death from infected ulcer	1%	
Probability of gangrene from infected ulcer	1%	
Probability of infected ulcer from uninfected ulcer	14%	
Probability of death from uninfected ulcer	0%	
Probability uninfected ulcer from infect ulcer	5%	
Probability of healed ulcer from uninfected ulcer	8%	
Probability of recurrent amputation	1%	Borkosky et al (2012)[63]
Probability of developing ulcer with neither neuropathy or PVD	0%	Ragnarson Tenvall et al (2001)[413]

Probability of developing ulcer with either neuropathy or PVD	1%	
Probability of developing ulcer with both neuropathy or PVD	1%	Persson et al (2000)[398]
Depression		
RR all cause death if depression	1.33	Egede et al (2005)[136]
RR CHF if depression	1.00	No data
RR MI if depression	1.00	No data
RR depression if neuropathy	3.10	Yoshida et al (2009)[533]
RR depression if stroke	6.30	Whyte et al (2004)[521]
RR depression if amputation	1.00	No data
Other probabilities		
Probability of severe visual loss from background diabetic retinopathy	1%	CORE default
Probability of reversal of neuropathy	0%	No data

Some clinical parameters in the model are dependent on other model parameters (such as baseline characteristics) and time (including age, duration of diabetes). These variables were all left unchanged from the CORE default values as they were based on the most relevant sources (such as the DCCT trial) and they had been through validation. **Error! Reference source not found.** simply eports the sources for the transition probabilities as described in the CORE model but the full set of probabilities is not reported.

Table 75: Clinical database - clinical progression parameters (transition probabilities)

Input variable	Dependent variable	Source/comment
Renal disease		
Probability onset micro-albuminuria	Duration of diabetes	DCCT [490]
Probability micro-albuminuria worsen to gross-proteinuria	Duration of diabetes	
Probability gross-proteinuria to end stage renal disease	Duration of gross-proteinuria	Rosolowsky et al (2011)[438]
Proportion end stage renal disease having: haemodialysis, peritoneal dialysis, renal transplant	Current age	U.S. Renal Data System, USRDS 2010[499]
Probability of death with end stage renal disease	Current age	

Input variable	Dependent variable	Source/comment
if under haemodialysis, peritoneal dialysis, or renal transplant		
Eye disease		
Probability onset background diabetic retinopathy/macular oedema/severe visual loss	Duration of diabetes	DCCT [490]
Probability onset of cataract extraction - male/female	Current age	Janghorbani et al (2000)[232]
Probability recurrent cataract extraction - male/female	Current age	
Neuropathy		
Probability onset neuropathy	Duration of diabetes	DCCT (2005) [456]
Health Failure		
Probability HF long-term mortality, gender and age dependent	Time since onset of CHF	Ho et al (1993)[214]
Myocardial infarction		
Probability death within 12 month after 1st MI, male/female, initial/recurrent	Current age	Malmberg et al (1995)[303] Herlitz et al (1996)[204]
Probability post MI long-term mortality, male/female	Time since 1st MI	
Stroke		
Probability death within 12 month after 1st or recurrent stroke, male/female	Current age	Eriksson et al (2001)[141]
Probability post stroke long-term mortality, male/female	Time since 1st stroke	
Probability recurrent stroke, male/female	Time since 1st stroke	
Depression		
Probability onset depression in males/females	Time of simulation	Golden et al (2008)[171]
Probability depression reversal for patients receiving/not receiving anti-depression program	Time of simulation	Valenstein et al (2001)[501]
Non-specific mortality		
Probability non-specific mortality	Current age, sex, race	Centers for Disease Control and Prevention, National Center for Health Statistics (2012)[79]
Physiological		

Input variable	Dependent variable	Source/comment
HbA1c progression	Time of simulation (0.045 per year)	DCCT [6]
BMI/HDL/LDL/SBP/Total-Cholesterol/TAG progression	Time of simulation	CORE Default
Quality of life adjustment based on current BMI[(a)]	BMI	Bagust et al (2005)[44]
Age adjustment for MI mortality	Current age	Herlitz et al (1996)[204]

Although BMI was part of the CORE model and we reported in the tables above the values linked to this parameter, none of our analyses uses BMI as an outcome. This is because the GDG did not select this as a critical outcome in the review protocols and this is justified by the fact that weight gain or loss is not as important for type 1 diabetes as it is for example for type 2 diabetes.

e) Treatment

Among the modules in the CORE model, this was the only one that was different for each of the three analyses conducted for this guideline. In this module the effectiveness and costs of the strategies compared in the analysis are defined.

The main changes applied to this module were on the HbA1c level and the hypoglycaemic events rate. In the base case, in the years subsequent to the treatment change, the annual progression of 0.045% in HbA1c (based on the DCCT study)[490] was applied (not the first year effect). This was changed in a sensitivity analysis where no annual progression was assumed.

Intensive glycaemic control based on the DCCT study was selected as opposed to standard glycaemic control which determined the transition probabilities.

Baseline event rates

Two outcomes were used to characterise treatment effectiveness: reduction in HbA1c and number of sever/major hypoglycaemic events. The GDG considered that HbA1c and severe/major hypoglycaemia were the most important (critical) clinical outcomes for assessing the efficacy of long-acting insulin treatment.

The cohort baseline HbA1c level was based on the National Diabetes Audit data for UK adult population with type 1 diabetes (8.6 %).[18]

No baseline value for hypoglycaemic event rate was required in the model as in the CORE model this is only a treatment-specific parameter and no baseline value is required.

Treatment effects

Treatment effects for both outcomes included in the model were based on the network meta-analysis (NMA) of the clinical evidence identified in the systematic review undertaken for the guideline. Model inputs were validated with clinical members of the GDG.

Appendix M includes details of the NMA undertaken to inform the cost effectiveness analysis. Two comparators that were evaluated in the NMA (detemir once/twice and NPH oce/twice) were not included in the economic analysis because it would not be possible to assign a correct cost to these

groups (it could be either the cost of once or twice). Therefore only those interventions where the type and frequency of insulin were specified were included in the economic analysis.

For the first outcome, reduction in HbA1c, the mean change from baseline, as obtained from the NMA (**Error! Reference source not found.**), was applied to the baseline value (8.6%) to specify the level of HbA1c achieved when using each of the model comparators.

Table 76: Mean change in HbA1c and standard error

Insulin	Change in HbA1c*	SE
Degludec (once daily)	-0.351	0.17
Detemir (once daily)	-0.395	0.13
Detemir (twice daily)	-0.483	0.10
Glargine (once daily)	-0.423	0.15
NPH (four times daily)	-0.008	0.17
NPH (once daily)	-0.281	0.17
NPH (twice daily)	-0.320	0.09

** Median of the posterior distribution for the mean change from the NMA.*

For the second outcome, number of severe/major hypoglycaemic events, the treatment effect was calculated using the event rates that were obtained from the NMA results. **Error! Reference source not found.** lists the treatment - specific event rates.

As NPH (four times daily) has not been included in the NMA for the severe/major hypoglycaemia outcome, it was assumed to have the same event rate as the NPH (twice daily).

Table 77: Event rates of severe/major hypoglycaemic events

	Event rate (per 100 patient years)*
Degludec (once daily)	50
Detemir (once daily)	61
Detemir (twice daily)	44
Glargine (once daily)	47
NPH (four times daily)	46
NPH (once daily)	54
NPH (twice daily)	46

** calculated using the median of the posterior distribution for the mean event rate from the NMA.*

Since there was high uncertainty around this outcome, for example the included studies showed high heterogeneity, in a sensitivity analysis we excluded this outcome from the model and we ran the analysis only with the HbA1c outcome.

It was discussed with the GDG whether quality of life values required any adjustment in those arms where injections were more frequent; however the GDG experts advised that this would not reflect real life as patients usually feel more in control if they inject more frequently and they also have multiple injections for example with short acting insulin.

Resource use and costs

Treatment-specific costs, that were likely to differ among the comparator insulin regimens, included the costs of the long-acting insulin and the needles. The cost of monitoring, nurse time and other

consumables are likely to be either the same or their differences are negligible regardless of the long-acting insulin or insulin regimen used. Hence, these costs were not included in the analysis.

Long acting insulin

The yearly cost of long-acting insulin treatment was calculated using nationally available prices from the BNF and MIMS June 2014[19 238] (**Error! Reference source not found.**). It was assumed that the total daily dose is the same for all insulin regimens (24 units/day). The impact of this was examined in a sensitivity analysis, where a daily dose of 20 units/day was used instead. Following discussions with the GDG, it was decided that only cartridges and pre-filled pens would be used to calculate LA insulin costs. Prices were largely the same for cartridges and pre-filled pens except for NPH. A simple average price was calculated using all available cartridges and pre-filled pens' prices.

Table 78: Long –acting insulin prices

Long-acting insulin	Product	Form[b]	Price
Insulin degludec	Tresiba®	5 x 3ml cartridges	£72.00[b]
		5 x 3ml FlexPen prefilled	£72.00[b]
		3 x 3ml FlexPen prefilled (200UI)	£86.40[b]
Insulin detemir	Levemir®	5 x 3ml cartridges	£42.00[c]
		5 x 3ml FlexPen prefilled	£42.00[c]
Insulin glargine	lantus®	5 x 3ml cartridges	£41.50[c]
		5 x 3ml SoloStar prefilled	£41.50[c]
		5 x 3ml cartridges	£41.50[c]
Insulin NPH			
	Highly purified animal		
	Hypurin® Bovine Isophane	5 x 3ml cartridges	£41.58[c]
	Hypurin® Porcine Isophane	5 x 3ml cartridges	£37.80[c]
	Human sequence		
	Insulatard®	5 x 3ml cartridges	£22.90[c]
	Humulin I®	5 x 3ml cartridges	£19.08[c]
		5 x 3ml KwikPen prefilled	£21.70[c]
	Insuman® Basal	5 x 3ml cartridges	£17.50[c]
		5 x 3ml SoloStar prefilled	£19.80[c]

(a) Strength of all cartridges and prefilled is 100IU unless otherwise stated
(b) Source: MIMS June 2014[19]
(c) Source: BNF June 2014[238]

Based on these prices, the total annual cost for each long-acting insulin was calculated. These costs are presented below, in **Error! Reference source not found.**.

Table 79: Annual costs of long-acting insulin per patient

Long acting insulin	Cost per unit	Yearly cost per patient (a)
Insulin degludec	£0.048	£420
Insulin detemir	£0.028	£245
Insulin glargine	£0.028	£242(b)
Insulin NPH	£0.017	£150

(a) Based on 24 units per day
(b) Different from yearly cost of insulin detemir due to rounding of cost per unit

Needles

The unit cost of the needles was calculated as a weighted average based on the prices of the 10 most commonly used needles, according to Prescription Cost Analysis, England data (**Error! Reference source not found.**).[200]

Table 80: The most commonly prescribed needles and their prices

Rank[a]	Needle	Cost per needle[a]	Number prescribed (million)[b]	% of total needles prescribed[b]
1	BD Microfine+ (5mm)	£0.13	73.1	21%
2	BD Microfine+ (8mm)	£0.09	62.5	18%
3	NovoFine (6mm)	£0.13	54.7	16%
4	NovoFine (8mm)	£0.09	47.5	14%
5	BD Microfine+ (4mm)	£0.13	39.9	12%
6	Mylife Clickfine (8mm)	£0.09	10.8	3%
7	Mylife Clickfine (6mm)	£0.13	10.1	3%
8	Unifine Pentips (8mm)	£0.08	6.3	2%
9	Unifine Pentips (6mm)	£0.12	5.9	2%
10	U100 Syrg Sle Use 0.5ml + 8mm Needle-Ster Hypod Syrg	£0.14	5.4	2%

(a) Drug Tariff 2013[368]
(b) Prescription Cost Analysis, England - 2013[200]

The weighted average needle cost was £0.11. This was used to calculate the annual cost of needles per patient for each long-acting insulin regimen, which varied according to the frequency of insulin administration. These costs are presented in **Error! Reference source not found.**.

Table 81: Annual cost of needles per patient

Long-acting insulin	Annual cost of needles per patient[a]
Degludec (once daily)	£39
Detemir (once daily)	£39
Detemir (twice daily)	£77
Glargine (once daily)	£39
NPH (four times daily)	£155
NPH (once daily)	£39
NPH (twice daily)	£77

(a) One needle is assumed to be used for each administration

Total cost

The annual treatment cost per patient (**Error! Reference source not found.**) was calculated as the sum of the long-acting insulin cost (calculated based on a daily dose of 24 units) and the cost of needles. These were assumed to accrue yearly from the initiation of insulin treatment, hence, were the same for first and subsequent years.

Table 82: Annual treatment cost per patient

Long-acting insulin	Annual treatment cost per patient
Degludec (once daily)	£459
Detemir (once daily)	£284

Long-acting insulin	Annual treatment cost per patient
Detemir (twice daily)	£323
Glargine (once daily)	£281
NPH (four times daily)	£305
NPH (once daily)	£189
NPH (twice daily)	£228

N.2.3 Computations

The CORE model data processor is programmed in C++ (Microsoft visual studio 6.0 Enterprise Edition). A combination of Markov model structure and Monte-Carlo simulation using tracker variables is used to capture the long-term, progressive nature of the disease and its complications. In Markov models, health states are mutually exclusive and the model is memoryless (that is, transition from one health state to another is not affected by patient history in the model. However, in real-life, diabetes complications are interlinked. The CORE model uses tracker variables to overcome this problem, allowing interaction between the complication sub-models. These sub-models run simultaneously and in parallel, which means that the patient can develop more than one complication within each cycle. Where a relevant link has been established, the development of one complication can influence transition probabilities in other sub-models. [389]

First and second order Monte-Carlo simulations with or without input parameter distributions are used in the model. Non-parametric bootstrap methods are used to evaluate uncertainty. The IMS CORE model has been described in more detail elsewhere.[389]

A closed cohort simulation approach was used, where a cohort with the specified baseline characteristics was defined. This cohort was simulated until the defined time horizon (80 years) is reached or until all patients in the cohort have died.Error! Reference source not found.**Error! eference source not found.** outlines the analysis process. In the base case probabilistic analysis the second order Monte Carlo simulation was selected and parameter distributions were used to account for parameter uncertainty. All sensitivity analyses were run without the second order sampling option.
Utilities and costs have been attached to each health state in the model, so QALYs can be calculated. QALYs were then discounted to reflect time preference (discount rate = 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. Costs were discounted to reflect time preference (discount rate = 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$	Where: *r*=discount rate per annum *n*=time (years)

The total cost and QALYs accrued by the cohort were divided by the number of patients in the population to calculate a mean cost and mean QALY per patient.

N.2.4 Sensitivity analyses

A number of sensitivity analyses were undertaken to test the robustness of the model results:

SA1 - HbA1c progression

In the base case analysis, the CORE model default value for the annual progression in HbA1c was used (0.045%). An alternative assumption of no annual progression in HbA1c level (0%) was tested.

Based on the GDG clinical experience, HbA1c levels in type 1 diabetes patients tend to be stable, unlike the case in type 2 diabetes patients.

SA2 - Utility estimation approach

In the base case analysis, the CORE model default "minimum approach" to calculating utility was used. In this approach, the quality of life for patients with multiple complications is assumed to take the minimum of the utility values associated with these complications. An alternative "multiplicative approach" was tested whereby utility for these patients is calculated as a multiplicative function of the utilities for these complications.

SA3 - Rate of severe/major hypoglycaemic events

In the base case analysis, the rates of severe/major hypoglycaemic events were based on the treatment-specific data from the NMA.

Since there was a lot of uncertainty around this outcome and the NMA did not show any significant difference in hypo event rates between treatments, in a sensitivity analysis we assumed no differential effect for any of the comparators on hypoglycaemic event rate, effectively considering HbA1c as the only clinical effectiveness measure. The rate used for all the treatment was that of NPH twice (46 events per 100 patient-year).

SA4 - Cohort characteristics

In the base case analysis, the simulated cohort representedthe average population with type 1 diabetes in the UK). A scenario analysis was run assuming a cohort representing a population in the UK with a more recent diagnosis of type 1 diabetes. The alternative cohort characteristics are reported in the table below.

Table 83: Cohort characteristics in SA4

Input variable	Value
Start age (years)	27
Duration of diabetes (years)	9.10
Proportion Male	55.2%
HbA1c (-points)	9.3%
Systolic Blood Pressure (mmHg)	121.48
Body mass index (BMI) (kg/m^2)	24.90
Proportion smoker	26%

SA5 - Mortality of major hypoglycaemic events

The base case mortality due to severe/major hypoglycaemia was varied in a one-way sensitivity analysis within a range between 0% and 5%. 5% was considered an extremely high value by the GDG.

SA6 - Utility of major hypoglycaemic events

The base case value (-0.012) was based on an adjustment made to the value reported in the study by Currie et al (2006).[104] The original higher value of -0.047 has been used as the upper value in our one-way sensitivity analysis where this parameter was varied within -0.047 and 0.

SA7 - Discounting

The discount rate was varied to 1.5% for both costs and benefits.

SA8 - Insulin daily dose

Insulin daily dose was reduced to 20 units/day (base case value was 24 units/day). The effectiveness was assumed to be the same, however the annual costs of strategies changed as reported in the table below.

Table 84: Annual cost of insulin treatment in SA8 – 20 units/day

Insulin type	Annual cost of needles[(a)]	Annual cost of insulin (20 units/day)[(b)]	Total annual cost
NPH once	£125.39	£38.65	£164.05
NPH twice	£125.39	£77.31	£202.70
NPH four times	£125.39	£154.61	£280.01
Glargine once	£201.97	£38.65	£240.62
Detemir once	£204.40	£38.65	£243.05
Detemir twice	£204.40	£77.31	£281.71
Degludec once	£350.40	£38.65	£389.05

(a) Based on Drug Tariff 2013[368] and Prescription Cost Analysis, England - 2013[200]
(b) Based on MIMS June 2014[19] and BNF June 2014[238]

N.2.5 Model validation

The analysis was developed in consultation with the GDG; model inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations. The detailed working of the model could not be checked by the NCGC economists but the IMS CORE diabetes model has undergone an extensive validation (by IMS and an external validator)[321] and results from the model have been widely published, with over 80 peer-reviewed publications.

N.2.6 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a

comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = (QALYs(X) \times \lambda) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each regimen are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

N.2.7 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[363] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have seven comparators, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY gained.

N.3 Results

N.3.1 Base case

Table 85 presents the results of the base case probabilistic analysis.

Table 85 – Probabilistic base case analysis results (mean per patient)

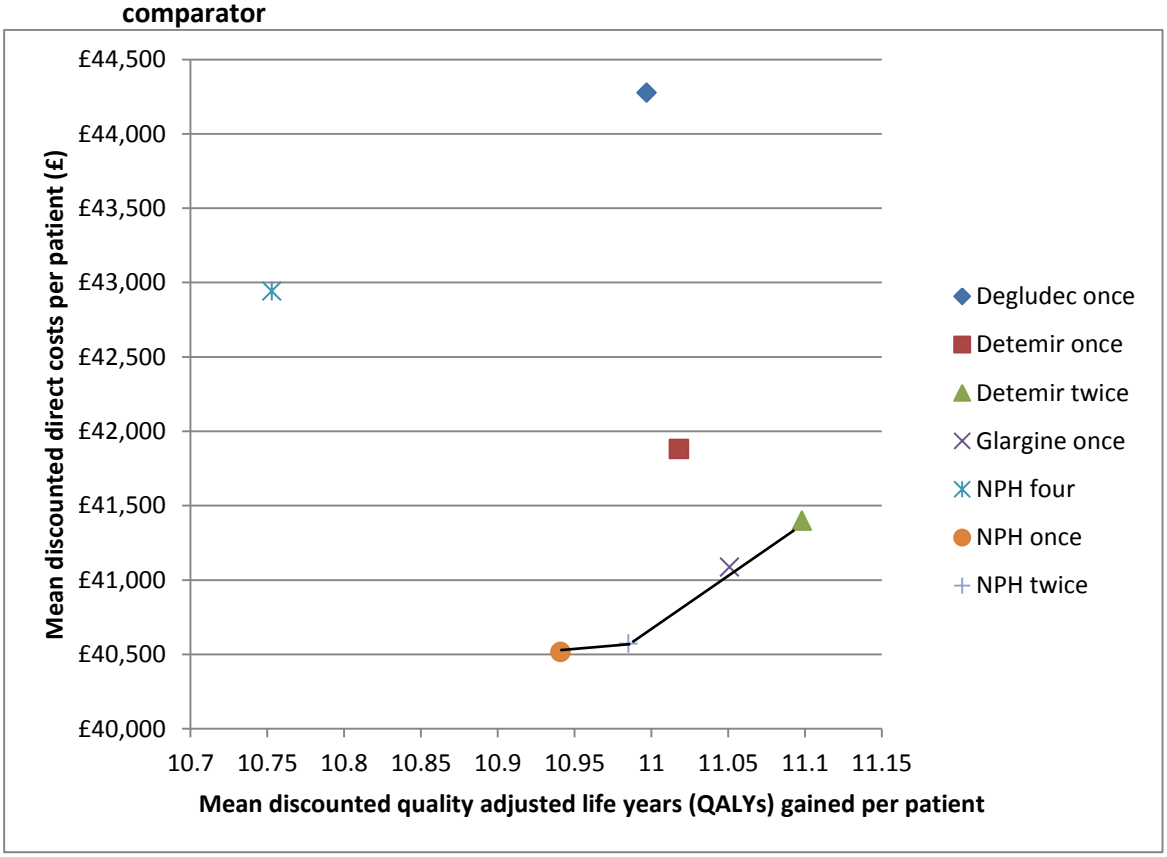
Insulin	Costs[a]	QALYs[b]	NMB[c]	Rank[d]
Degludec (once daily)	£44,276	10.997	£175,664	6
Detemir (once daily)	£41,881	11.02	£178,479	4
Detemir (twice daily)	£41,398	11.098	£180,562	1
Glargine (once daily)	£41,087	11.051	£179,933	2
NPH (four times daily)	£42,941	10.753	£172,119	7
NPH (once daily)	£40,516	10.941	£178,304	5
NPH (twice daily)	£40,573	10.985	£179,127	3

(a) Discounted life-time costs per patient
(b) Discounted life-time quality-adjusted life years (QALYs) per patient
(c) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(d) Ranked in descending order according to NMB

According to the probabilistic analysis, the optimal strategy at the £20,000 per QALY threshold is detemir twice daily, which is also the most effective strategy. This strategy dominates, ie it is more effective and less costly, compared to three strategies: Degludec once, Detemir once and NPH four

times daily. It is more costly and more effective than glargine once daily, NPH once daily and NPH twice daily. At a cost-effectiveness threshold of £20,000 per QALY gained, this increased effectiveness justifies the increase in costs. The total costs and QALYs gained associated with the use of each comparator are presented on the cost effectiveness plane shown in **Error! Reference source ot found.** together with the incremental analysis results.

Figure 261: Cost effectiveness plane illustrating total costs and QALYs gained for each comparator



Degludec once, NPH four and Detemir once are dominated strategies.Glargine once is extendedly dominated by a combination of NPH twice and detemir twice; however if detemir twice was not available, the ICER of glargine once compared to NPH twice would be £7,788 per QALY, hence glargine would be the preferred option. Excluding the dominated options, the ICER from comparing NPH twice to NPH once is £1,295 per QALY. The ICER from comparing detemir twice to NPH twice is £7,300 per QALY.

Error! Reference source not found. illustrates overall survival for the different long-acting insulin egimen. The results show that the use of insulin detemir twice daily was associated with the highest survival while the use of insulin NPH four times daily was associated with the lowest overall survival.

Figure 262: Overall survival according to long-acting insulin strategy

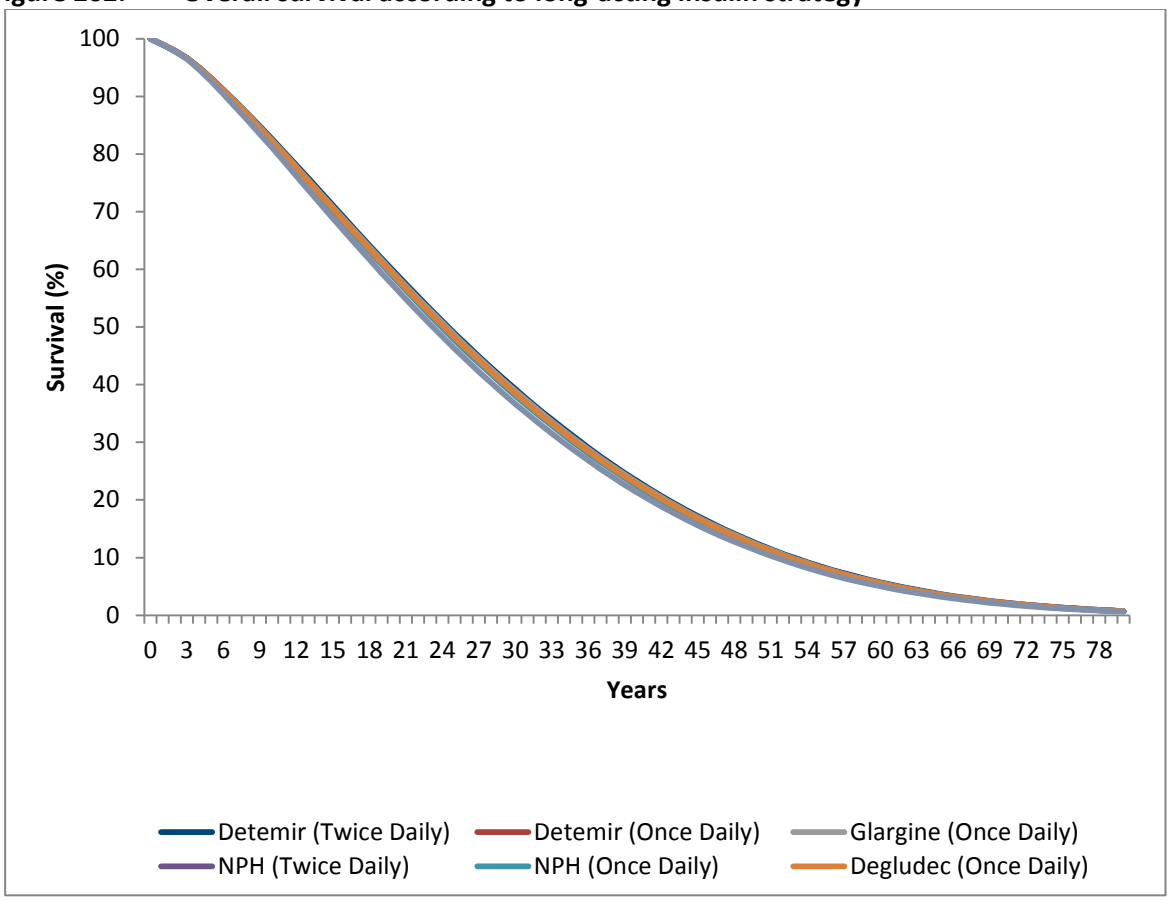


Table 86 presents the breakdown of the life-time costs per patient to its main categories.

Table 86: Breakdown of mean direct costs per patient by category

Insulin / Category	Detemir (twice daily)	Glargine (once daily)	NPH (twice daily)	Detemir (once daily)	NPH (once daily)	Degludec (once daily)	NPH (four times daily)
Treatment	**£5,081**	**£4,412**	**£3,558**	**£4,451**	**£2,946**	**£7,180**	**£4,682**
Management	**£1,773**	**£1,766**	**£1,756**	**£1,763**	**£1,751**	**£1,758**	**£1,723**
Hypoglycaemia	**£2,391**	**£2,508**	**£2,454**	**£3,050**	**£2,770**	**£2,623**	**£2,410**
Cardiovascular diseases	£3,082	£3,096	£3,098	£3,100	£3,101	£3,081	£3,122
Renal	£11,572	£11,699	£11,972	£11,784	£12,120	£11,938	£12,809
Ulcer/Amputation/ Neuropathy	£10,543	£10,627	£10,724	£10,701	£10,778	£10,703	£11,031
Eye-related complications	£5,810	£5,833	£5,867	£5,886	£5,909	£5,849	£6,027
Anti-Depression Treatment	£1,147	£1,146	£1,145	£1,145	£1,142	£1,145	£1,137
Total complications	**£32,154**	**£32,401**	**£32,806**	**£32,616**	**£33,050**	**£32,716**	**£34,126**
Total Costs	**£41,398**	**£41,087**	**£40,573**	**£41,881**	**£40,516**	**£44,276**	**£42,941**

The results show that the use of insulin detemir twice daily generated a mean direct cost that is higher than using insulin glargine once daily, insulin NPH twice daily or insulin NPH once daily. This was mainly driven by the higher cost associated with treatment (£5,081) and also due to the higher survival in patients treated with insulin detemir twice daily. However, the total costs of treating renal complications, ulcer/amputation/neuropathy and eye-related complications were lower when using insulin detemir twice compared to these insulin regimens. In fact, the use of insulin detemir twice daily was associated with the lowest cost across all comparators in these categories and in the total cost of managing all complications (£32,154). This is likely to be due to the better control of HbA1c achieved when using insulin detemir twice daily.

The total cost of using insulin degludec was the highest among the comparators. This was primarily driven by the highest cost of treatment (£7,180).

Although overall the QALYs and costs estimates were higher than in the probabilistic base case analysis, the deterministic analysis results Table 87 showed the same results in terms of ranking as the probabilistic analysis.

Table 87: Deterministic results (mean per patient)

Insulin	Costs[a]	QALYs[b]	NMB[c]	Rank[d]
Degludec once	£46,955	12.358	£200,205	6
Detemir once	£43,976	12.38	£203,604	4
Detemir twice	£43,296	12.484	£206,384	1
Glargine once	£42,962	12.427	£205,578	2
NPH four	£46,402	12.091	£195,418	7
NPH once	£42,629	12.294	£203,251	5
NPH twice	£42,925	12.34	£203,875	3

(a) Discounted life-time costs per patient
(b) Discounted life-time quality-adjusted life years (QALYs) per patient
(c) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(d) Ranked in descending order according to NMB

N.3.2 Sensitivity analyses

A wide range of sensitivity analyses were undertaken in which key assumptions and parameters were varied. These are explained in N.2.4 and the main conclusions are listed in Table 88

Table 88: Results of sensitivity analyses

	Changes in ranking
Sensitivity analyses	
SA1: HbA1c progression	No change
SA2: utility estimation approach	No change
SA3: rate of severe/major hypoglycaemic events	1 - Detemir twice (no change) 2 – Glargine once (no change) 3 - Detemir once (from 4) 4 – NPH twice (from 3) 5 – NPH once (no change) 6 – NPH four times (from 7) 7 – Degludec (from 6)
SA4: cohort characteristics	No change
SA5: mortality of major hypoglycaemic events	When mortality was 3% or more: 1 - Detemir twice (no change)

	2 – Glargine once (no change) 3 – NPH twice (no change) 4 – NPH once (from 5) 5 - Detemir once (from 4) 6 – Degludec (no change) 7 – NPH four times (no change)
SA6: disutility of major hypoglycaemic events	When disutility was increased to 0: 1 - Detemir twice (no change) 2 – Glargine once (no change) 3 – Detemir once (from 4) 4 - NPH twice (from 3) 5 – NPH once (no change) 6 – Degludec (no change) 7 – NPH four times (no change) When disutility was decreased to at least -0.0376: 1 - Detemir twice (no change) 2 – Glargine once (no change) 3 – NPH twice (no change) 4 – NPH once (from 5) 5 - Detemir once (from 4) 6 – Degludec (no change) 7 – NPH four times (no change)
SA7: discounting	No change
SA8: insulin daily dose	No change

The results of the one-way sensitivity analyses showed that the model is robust to many changes in the parameters in terms of the best ranking strategy. Changing the disutility of mortality due to major hypoglycaemic events did not change the first two optimal interventions. There was only some changes in the ranking of less effective interventions.

A sensitivity analysis considering expected changes in insulin detemir and insulin glargine prices was also considered but not undertaken, given the uncertainty around the magnitude of price reduction expected.

N.4 Discussion

N.4.1 Summary of results

The base case probabilistic and deterministic analyses results show that insulin detemir twice daily is the most clinically effective, with the highest mean QALYs gained over life-time horizon. It was the also the optimal choice in terms of cost-effectiveness, offering the highest NMB compared with all other long-acting insulin regimens. This was confirmed in all the sensitivity analyses conducted. Glargine once was the second ranking in both probabilistic and determinstc analyses and this raking was changed only in one sensitivity analysis based on the NMA results where arms were allocated to a specific frequency even when in reality a mix of frequencies were used in the RCTs. In this analysis NPH twice became the second ranking strategy while glargine was the third best option.

In relation to the frequency of administration, twice daily regimens appeared to be more effective and overall cost effective compared to once daily regimen; where these options were available for

the same long-acting insulin (insulin NPH and insulin detemir). Twice daily insulin detemir had higher NMB than the once daily regimen in the deterministic analysis and all sensitivity analyses. Similarly, twice daily regimen of insulin NPH had a higher NMB than the once daily option. Conversely NPH four times daily was both more costly and less effective than the twice daily administration and therefore offering this option would not represent an efficient use of the NHS resources.

Parameters of particular uncertainty were mortality and disutility associated with severe/major hypoglycaemic events. The model was robust to changes in these parameters for the first two ranking positions.

N.4.2 Limitations and interpretation

There is, inevitably, uncertainty around the model parameter inputs, and in the probabilistic analysis, the cost effectiveness of insulin detemir twice daily was reduced compared to the deterministic analysis. However, the model results were tested in a wide range of sensitivity analyses which showed that the optimal choice (insulin detemir twice daily) was the most cost effective at the £20,000 per QALY gained threshold. There was less certainty around the choice of the second and third best options, where insulin insulin glargine once daily was most likely the second best option.

This original economic analysis is based on many parameters that are not specific to a type 1 diabetes population but utilises data on the type 2 population as well. It also utilises reduction in HbA1c as one of two main clinical outcome measures which is an intermediate outcome measure; however this is considered to be a reliable proxy measure of disease progression and complications outcomes. Its link to the most important clinical outcomes for diabetes patients is already well established and validated.

Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, it was believed that the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.[104]

Patient adherence and any disutility due to multiple daily injections were not included in the model. However, the GDG members believed that type 1 diabetes patients generally prefer to be in control by having multiple daily injections and this would reduce their fear of hypoglycaemia, with no negative effect on the treatment adherence or quality of life.

Another limitation of our analysis is that the correlation between the treatment effects obtained with the NMA could not be kept when running the economic model as the analyses were run as pairwise comparison. Therefore in the probabilistic analyses the correlation between effect parameters is not taken into account. Generalisability to other populations or settings

This original economic analysis is directly applicable to the UK adult type 1 diabetes population. Generalisability of its findings to the paediatric type 1 diabetes population or populations or settings not included in the guideline scope is not appropriate.

N.4.3 Comparisons with published studies

The results of this economic analysis are in line with the findings from five cost-utility analyses which found that insulin detemir was cost effective compared to NPH (ICERs: £2,500, £3,443, £9,526, £12,989 and £19,285 per QALY gained).[390,392,497,502,505]. They were also in agreement with findings from another three cost-utility analysis which found that insulin glargine was cost effective compared to NPH (ICERs: £3,496 - £4,978, £3,189 - £9-767 and £10,903 per QALY gained),[183,322,514]. The findings also agreed with the conclusions of another cost-utility analysis that found that insulin detemir was dominant (less costly and more effective) over insulin glargine, [505]. However, one of theeconomic evaluations identified, Cameronet al (2009), concluded that insulin glargine dominated insulin detemir.[73] This is likely to be due to the difference in the clinical effectiveness evidence used to

inform the models. In this study, the clinical effectiveness estimates used in the model were based on a direct meta-analysis combining results from trials that compared each of insulin glargine and insulin detemir versus insulin NPH. Its results showed that insulin glargine was more effective compared to insulin detemir in terms of HbA1c reduction (-0.11% versus -0.06%, respectively, compared to insulin NPH). IThis MA did not consider insulin detemir once and insulin detemir twice daily regimens separately; since in our model detemir twice is more cost effective than glargine but glargine is more cost effective than detemir once, the results in this study could be due to the lack of differentiation between the frequencies of administration in the detemir arm. n contrast, our economic analysis utilises clinical effectiveness estimates from NMA that combines the results of all available RCTs which compared any of the long-acting insulin regimens included in the model. The NMA takes into account frequency of administration of insulin detemir and provides estimates of clinical effectiveness for each regimen (once and twice daily) separately. No previous economic evaluations comparing once versus twice daily regimens of long-acting insulin NPH and insulin detemir were identified. Hence, this original economic analysis is the first to assess their comparative cost effectiveness.

N.4.4 Conclusions

According to the results of this original economic model based on the current clinical evidence review and GDG input, it is likely that insulin detemir twice daily is the most cost effective long-acting insulin regimen for people with type 1 diabetes. Insulin glargine once daily is likely to be cost effective for patients for whom insulin detemir twice daily regimen is not an option. This analysis is directly applicable, with minor limitations.

Similarly, this original economic analysis found that twice daily regimen is more cost effective compared to once daily regimen of both insulin detemir and insulin NPH. The same does not apply for higher administration frequency, where NPH four times daily was found to be dominated by the once and twice daily regimens of insulin NPH. This analysis is directly applicable with minor limitations.

N.4.5 Implications for future research

This original economic analysis showed that there is uncertainty around the health-related quality of life associated with major/severe hypoglycaemic events. Additionally, an accurate estimate of mortality from severe/major hypoglycaemia is not currently available. Further research is needed to reduce this uncertainty, given the sensitivity of the model results to these parameters. Evidence is also sparse for the newly approved long-acting insulin, insulin degludec, which is understandable given its recent entry into the market.

Appendix O: Cost-effectiveness analysis – HbA1c threshold

O.1 Introduction

The target HbA1c level was identified as a priority for original economic analysis because more aggressive HbA1c targets may be clinically desirable, however more resources may need to be devoted to achieve a lower threshold. The clinical review conducted for this guideline showed that with lower HbA1c values, the risk and incidence of clinical events (such as mortality, CVD, CHD, stroke, retinopathy, microalbinuria) was significantly reduced.

This economic evaluation seeks to provide information regarding the consequences in terms of expected long-term clinical benefits and cost savings to the NHS of attaining an HbA1c target of 6.5%. This evaluation does not look at the cost of any additional intervention required to achieve the targets lower than 7.5% (e.g. insulin pumps, education programmes etc); therefore the model does not inform cost-effectivess but informs only the consequences of attaining different HbA1c targets.

The review question linked to this high priority area is:

- In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?

No economic studies were found in the literature that looked at this question.

The following general principles were adhered to in developing the economic analysis:

- The GDG was consulted during the construction and interpretation of the model.
- When published data werenot available expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

O.2 Methods

O.2.1 Model overview

A previously published diabetes model that has been validated against real-life clinical and epidemiological data was used for the analysis (IMS CORE Diabetes Model (CDM)). The IMS CDM is an internet-based, interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. The type 1 diabetes data were selected for running our analysis.

O.2.1.1 Comparators

The GDG decided to compare the current target of 7.5% with a target of 6.5 % on the grounds that a minimal risk of retinopathy was achieved at this level, with further improvements in HbA1c not achieving any further significant reduction in retinopathy risk (see clinical evidence review conducted for this guideline in chapter 9.1.2 of the Full Guideline). A secondary analysis compared a target of HbA1c of 7.0% versus 7.5%.

O.2.1.2 Population

The base case (primary analysis) considered a cohort of adults representing the average individuals with type 1 diabetes in the UK. In a sensitivity analysis, data representing a population with a more recent diagnosis oftype 1 diabetes in the UK were selected.

O.2.1.3 Time horizon, perspective, discount rates used

A time horizon of 80 years was used in the base case as this was deemed sufficient to consider lifetime costs and outcomes (note that in the CORE model a number of years has to be specified to define the time horizon). Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, however it deviates from the reference case in that an incremental analysis was not conducted as the costs to achieve different target levels are not considered; since different interventions could be provided to achieve the lower target, it would not be possible to estimate this cost. Even if a threshold analysis was conducted to estimate the maximum cost that we would be willing to pay (based on the cost-effectiveness threshold of £20,000per QALY) this would rely on the assumption that interventions provided to achieve the lower threshold are 100% effective (ie all the patients to whom the interventions are provided achieve a target of 6.5%). For this reasons it would be misleading to estimate an incremental cost effectiveness ratio or to conduct a threshold analysis.[365] A sensitivity analysis using a discount rate of 1.5% for both costs and health benefits is conducted.

O.2.2 Approach to modelling

O.2.2.1 Model structure

The CORE Diabetes Model is a validated, non-product specific diabetes policy analysis tool that allows performing economic analyses of interventions used in diabetes using a series of interlinked, inter-dependent sub-models which simulate the following diabetes complications:

- angina,
- myocardial infarction,
- congestive heart failure,
- stroke,
- peripheral vascular disease,
- diabetic retinopathy,
- macular oedema,
- cataract,
- hypoglycaemia,
- ketoacidosis,
- lactic acidosis,
- nephropathy and end-stage renal disease,
- neuropathy,
- foot ulcer,
- amputation
- and non-specific mortality.

Each of these sub-models is a Markov model which uses time-, state- and diabetes type-dependent probabilities that have been derived from published sources. Interaction between the individual

complication sub-models is mediated through the use of Monte Carlo simulation using tracker variables.[389]

The core model has been validated extensively against epidemiological and clinical studies of type 1 diabetes. Full description of the CORE model and its modules and sub-models is given in Palmer et al (2004).[389]

O.2.2.2 Uncertainty

The CORE model could also be run probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 1000 times for the base case and results were summarised. Distributions around different parameters are set by default in the CORE model and these are explained in the document available on the CORE website.[227]

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- intervention costs

In addition, other deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

O.2.2.3 Summary of model inputs

The CORE model input parameters are grouped under the following input databases:

g. cohort
h. economics
i. other management
j. clinical
k. treatment
    i. clinical effectiveness
    ii. costs

The default model inputs for type 1 diabetes were validated with the clinical members of the GDG and, if found appropriate, were used. Where more reliable or recent UK sources were identified, these were used instead. Parameters for all the databases except for the treatment database were common to all the three analyses developed for this guideline. Treatment data (costs and effectiveness) differ between analyses as they were strategy-specific.

Details about the input parameters in the following databases are reported in Appendix N, section N.2.2.3:

l. cohort
m. economics
n. other management
o. clinical

Details about the treatment database are reported in the following paragraphs.

O.2.2.4 Treatment database

Among the modules in the CORE model, this was the only one that was different for each of the three analyses conducted for this guideline. In this module the effectiveness of the strategies compared in the analysis are defined.

The only parameter that was modified in this module was the HbA1c level which was set as equal to the target of the strategy. In the base case in the years subsequent to the treatment change, the annual progression of 0.045% in HbA1c (based on the DCCT study)[490] was applied. This was changed in a sensitivity analysis where no annual progression was assumed and the HbA1c level of each strategy was constant throughout the years.

Intensive glycaemic control based on the DCCT study was selected as opposed to standard glycaemic control which determined the transition probabilities.

Baseline event rates

The cohort baseline HbA1c level was based on the National Diabetes Audit data for UK adult population with type 1 diabetes (9.3%).[18]

The baseline hypoglycaemic event rate in the base case was 110/100 patient years for major hypos and 3550/100 patient years for minor hypos, based on the UK Hypoglycaemia Study Group.[16] No difference was assumed between strategies as there were no data available to assume a lower HbA1c target increases the risk of hypoglycaemic events.This was considered a limitation of the model as although some recent studies[243] reported a reduction in the risk of severe hypoglycaemia associated with lower levels of HbA1c, the risk is still present.

Resource use and costs

No costs were assigned to the strategies compared as a combination interventions could be used to achieve the HbA1c target level. Even if we had to assume a proportion of insulin pump therapy and education, for example, the effectiveness of these to reduce the HbA1c level would still be unknown and the cost thus estimated would not reflect the real effectiveness achieved.

O.2.3 Computations

Please see N.2.3.

O.2.4 Sensitivity analyses

A number of sensitivity analyses were undertaken to assess the changes in costs and QALYs when different assumptions were made. The sensitivity analyses were conducted deterministically.

SA1: Alternative HbA1cb target

In this analysis a target of 7.0% was the intervention compared with the current target of 7.5%.

SA2: No annual HbA1c progression

In the base case analysis, the CORE model default value for the annual progression in HbA1c was used (0.045%). An alternative assumption of no annual progression in HbA1c level (0%) was tested. Based on the GDG clinical experience, HbA1c levels in type 1 diabetes patients tend to be stable, unlike the case in type 2 diabetes patients.

SA3: Utility estimation method

In the base case analysis, the CORE model default "minimum approach" to calculating utility was used. In this approach, the quality of life for patient with multiple complications is assumed to take the minimum of the utility values associated with these complications. An alternative "multiplicative approach" was tested whereby utility for these patients is calculated as a multiplicative function of the utilities for these complications.

SA4: Discount rate

The discount rate was varied to 1.5% for both costs and benefits.

SA5: Cohort characteristics

In the base case analysis, the simulated cohort representedthe average population with type 1 diabetes in the UK). A scenario analysis was run assuming a cohort representing a population in the UK with a more recent diagnosis of type 1 diabetes. The alternative cohort characteristics are reported in **Error! Reference source not found.** in Appendix N.

O.2.5 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed amongst the GDG for expert clinical validation.

The model was checked by the health economist undertaking the analysis with a focus on the selection of input parameters for the web-based model, and was then check by a second experienced health economist. The detailed working of the model could not be checked by the NCGC economists but the IMS CORE diabetes model has undergone an extensive validation (by IMS and an external validator)[321] and results from the model have been widely published, with over 80 peer-reviewed publications.

O.2.6 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[359] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In this analysis no incremental cost effectiveness was estimated and it was not possible to apply the usual NICE criteria to determine the cost effectiveness of the interventions compared. The expected QALY gain and cost savings associated with the lower HbA1c target were considered by the GDG when making recommendations together with some considerations on the possible resources required to achive that target.

O.3 Results

O.3.1 Base case summary results

The mean costs and health outcomes associated with each strategy are reported in Table 89 below. The difference column shows the health gain and the cost savings (negative figure) per patients associated with the 6.5% target strategy (0.79 QALY and £11,274 over 80 years).

Table 89: Probabilistic results (mean per patient)

	HbA1c 6.5%		HbA1c 7.5%		Difference
	Mean	SD (low – high 95% CI)	Mean	SD (low – high 95% CI)	

	HbA1c 6.5%		HbA1c 7.5%		Difference
Life expectancy - undiscounted years (SD, low 95% CI – high 95% CI)	31.627	12.669 (30.842 - 32.412)	29.752	12.658 (28.967 - 30.536)	1.875
Life expectancy - discounted years (SD, low 95% CI – high 95% CI)	16.952	4.305 (16.685 - 17.218)	16.308	4.472 (16.031 - 16.586)	0.644
QALYs undiscounted (SD, low 95% CI – high 95% CI)	22.799	9.367 (22.218 - 23.38)	21.314	9.359 (20.734 - 21.894)	1.485
QALYs discounted (SD, low 95% CI – high 95% CI)	12.429	3.335 (12.223 - 12.636)	11.875	3.462 (11.66 - 12.089)	0.554
Direct Costs discounted (£) (SD, low 95% CI – high 95% CI)	29,908	18,739 (28,746 – 31,069)	33,432	20,272 (32,176 – 34,689)	-3,524

The undiscounted values are quite high compared to the discounted outcomes as many of the benefits of the 6.5% strategy are experiences later in the patient's life through averted diabetes-related complications and subsequent deaths. The model was also run deterministically (Table 90). The determinstc analysis was more favourable to the lower target as its effectiveness and cost savings were larger. This could be due to the non-linearity of Markov models.

Table 90: Deterministic results (mean per patient)

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy - undiscounted years	35.342	32.936	0.703
Life expectancy - discounted years	18.989	18.286	0.744
QALYs undiscounted	25.769	23.617	2.406
QALYs discounted	14.121	13.377	2.152
Direct Costs discounted (£)	24,372	31,102	-6,730

Table 91 shows the difference in each cost component of the model: there are cost savings due to fewer complications in the 6.5% target strategy while overall the management, hypoglycaemia and anti-depression treatment costs are higher because more people are alive and accrue these costs.

Table 91: Disaggregated cost to the NHS (£)

	HbA1c 6.5%	HbA1c 7.5%	Difference
Treatment	0	0	0
Management	1,971	1,896	75

CVD	2,802	2,947	-145
Renal	6,147	8,203	-2,056
Ulcer/ Amputation/ Neuropathy	8,367	9,355	-988
Eye	4,511	5,099	-588
Hypoglycaemia	4,960	4,778	182
Anti-depression treatment	1,149	1,154	-5
Total Costs	**29,908**	**33,432**	**-3,524**

O.3.2 Sensitivity analyses

The base case results were tested by conducting a series of sensitivity analyses run probabilistically which have been described in O.2.3. Results of these analyses are reported in the tables below.

Table 92: SA1 – Alternative HbA1c target

	HbA1c 7.0%	HbA1c 7.5%	Difference
Life expectancy (undiscounted years)	30.715	29.752	0.963
Life expectancy (discounted years)	16.644	16.308	0.336
QALYs (undiscounted)	22.073	21.314	0.759
QALYs (discounted)	12.162	11.875	0.287
Direct Costs (£) (discounted)	31,642	33,432	-1,790

Table 93: SA2 – No annual HbA1c progression

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy (undiscounted years)	33.629	31.711	1.918
Life expectancy (discounted years)	17.394	16.766	0.628
QALYs (undiscounted)	24.396	22.844	1.552
QALYs (discounted)	12.804	12.25	0.554
Direct Costs (£) (discounted)	28,207	31,866	-3,659

Table 94: SA3 – Utility estimation method

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy (undiscounted years)	31.627	29.752	1.875
Life expectancy (discounted years)	16.952	16.308	0.644
QALYs (undiscounted)	21.575	19.972	1.603
QALYs (discounted)	12.006	11.366	0.64
Direct Costs (£) (discounted)	29,908	33,432	-3,524

Table 95: SA4 – Discount rate (1.5% for both costs and effects)

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy (undiscounted years)	31.627	29.752	1.875

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy (discounted years)	23.43	22.29	1.14
QALYs (undiscounted)	22.799	21.314	1.485
QALYs (discounted)	17.03	16.094	0.936
Direct Costs (£) (discounted)	47,864	52,325	-4,461

Table 96: SA5 – Cohort characteristics

	HbA1c 6.5%	HbA1c 7.5%	Difference
Life expectancy (undiscounted years)	39.002	36.314	2.688
Life expectancy (discounted years)	19.322	18.468	0.854
QALYs (undiscounted)	28.195	26.1	2.095
QALYs (discounted)	14.221	13.502	0.719
Direct Costs (£) (discounted)	39,841	43,787	-3,946

O.4 Discussion

O.4.1 Summary of results

Achieving a target of 6.5% HbA1c compared to a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524, when only the consequences of the HbA1c reduction in terms of reduction of complications are considered. The actual costs of strategies that have to be implemented to achieve this target have not been considered and could offset the cost savings.

O.4.2 Limitations and interpretation

The cost of any additional intervention(s) used to achieve the lower target is not included. Therefore this analysis does not give information about which interventions would be cost-effective in the achievement of a lower HbA1c target, and it does not conclude whether the lower target is cost-effective at all.

This original economic analysis is based on many parameters that are not specific to a type 1 diabetes population but utilises data on the type 2 population as well. It also utilises reduction in HbA1c as one of two main clinical outcome measures which is an intermediate outcome measure; however this is considered to be a reliable proxy measure of disease progression and complications outcomes. Its link to the most important clinical outcomes for diabetes patients is already well established and validated.

Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, it was believed that the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.[104] Also the potential increased risk of hypo events associated with a lower target level has not been taken into account in the analysis. This could have led to an overestimation of the QALY gain and cost savings associated with the lower target.

O.4.3 Generalisability to other populations

This original economic analysis is directly applicable to the UK adult type 1 diabetes population. Generalisability of its findings to the paediatric type 1 diabetes population or populations or settings not included in the guideline scope is not appropriate.

O.4.4 Comparisons with published studies

No existing economic evidence was identified in the published literature.

Appendix P: Cost-effectiveness analysis – Continuous glucose monitoring (CGM) versus standard monitoring of blood glucose (SMBG)

P.1 Introduction

The GDG identified the comparison of continuous glucose monitoring (CGM) with standard monitoring of blood glucose (SMBG) in different frequencies as a high priority area for economic analysis. Different frequencies of SMBG and in particular CGM have different costs and may result in different outcomes for patients with type 1 diabetes.

The review questions linked to this high priority area are:

- In adults with type 1 diabetes, what is optimum frequency to self-monitor blood glucose for effective glucose/diabetic control?
- In adults with type 1 diabetes, is real-time CGM more effective than SMBG for optimum diabetic control?

A systematic review of the clinical literature was conducted as part of this guideline (see chapter xx) and this informed the economic analysis.

In the economic literature review, two economic evaluations were included that addressed the second question. [226,325] Details of these studies are included in the full guideline (see Chapter 9). They both concluded that CGM is not cost effective compared to SMBG but they both were partially applicable with potentially serious limitations.

The review did not identify any economic evaluations that addressed the first review question on the frequencies of SMBG. Given the importance of these questions in terms of both costs and health benefits, the uncertainty and the poor quality of the available evidence, an original economic analysis was deemed necessary.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- The GDG was consulted during the construction and interpretation of the model.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

P.2 Methods

P.2.1 Model overview

A previously published diabetes model that has been validated against real-life clinical and epidemiological data was used for the analysis (IMS CORE Diabetes Model (CDM)). The IMS CDM is an internet-based, interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist,

facilitating running diabetes type-specific analysis. The type 1 diabetes data were selected for running our analysis.

P.2.1.1 Comparators

Strategies compared in the model included different frequencies of SMBG and continuous glucose monitoring (CGM), specifically:

p. SMBG twice a day
q. SMBG 4 times a day
r. SMBG 6 times a day
s. SMBG 8 times a day
t. SMBG 10 times a day
u. CGM (real-time)

Retrospective CGM was included in the original review question however the clinical evidence did not show any benefits over SMBG and therefore it was excluded from this model as it was not an option for recommendations. Based on the GDG expert opinion we considered SMBG 4 times a day as the current practice.

P.2.1.2 Population

The base case (primary analysis) considered a cohort of adults representing the average individuals with type 1 diabetes in the UK. In a sensitivity analysis, data representing a population with a more recent diagnosis oftype 1 diabetes in the UK were selected.

P.2.1.3 Time horizon, perspective, discount rates used

A time horizon of 80 years was used in the base case as this was deemed sufficient to consider lifetime costs and outcomes (note that in the CORE model a number of years has to be specified to define the time horizon). Costs and quality-adjusted life years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.[365] A sensitivity analysis using a discount rate of 1.5% for both costs and health benefits was conducted.

P.2.2 Approach to modelling

P.2.2.1 Model structure

The CORE Diabetes Model is a validated, non-product specific diabetes policy analysis tool that allows performing real-time simulations taking into account the use of intensive or conventional insulin therapy, oral hypoglycaemic medications, screening and treatment strategies for microvascular complications, treatment strategy for end stage complications and multifactorial interventions.

It simulates diabetes progression using a series of 17 interlinked, inter-dependent sub-models which simulate the following diabetes complications:

- angina,
- myocardial infarction,
- congestive heart failure,
- stroke,
- peripheral vascular disease,

- diabetic retinopathy,
- macular oedema,
- cataract,
- hypoglycaemia,
- ketoacidosis,
- lactic acidosis,
- nephropathy and end-stage renal disease,
- neuropathy,
- foot ulcer,
- amputation
- and non-specific mortality.

Each of these sub-models is a Markov model which uses time-, state- and diabetes type-dependent probabilities that have been derived from published sources. Interaction between the individual complication sub-models is mediated through the use of Monte Carlo simulation using tracker variables.[389]

The core model has been validated extensively against epidemiological and clinical studies of type 1 diabetes. Full description of the CORE model and its modules and sub-models is given in Palmer et al (2004).[389]

P.2.2.2 Uncertainty

The CORE model could also be run probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly (1000 times) for the base case and results were summarised. Distributions around different parameters are set by default in the CORE model and these are explained in the document available on the CORE website.[227]

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- intervention costs

In addition, other deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

P.2.2.3 Summary of model inputs

The CORE model input parameters are grouped under the following input databases:

v. cohort
w. economics
x. other management
y. clinical
z. treatment
    i. clinical effectiveness

ii. costs

The default model inputs for type 1 diabetes were validated with the clinical members of the GDG and, if found appropriate, were used. Where more reliable or recent UK sources were identified, these were used instead. Parameters for all the databases except for the treatment database were common to all the three analyses developed for this guideline. Treatment data (costs and effectiveness) differ between analyses as they were strategy-specific.

Details about the input parameters in the following databases are reported in Appendix N, section N.2.2.3:

aa. cohort

bb. economics

cc. other management

dd. clinical

Details about the treatment database are reported in the following paragraphs.

P.2.2.4 Treatment

Among the modules in the CORE model, this was the only one that was different for each of the three analyses conducted for this guideline. In this module the effectiveness and costs of the strategies compared in the analysis are defined.

The parameters that were modified in this module were the HbA1c level and in a sensitivity analysis the hypoglycaemic events rate. In the base case in the years subsequent to the treatment change, the annual progression of 0.045% in HbA1c (based on the DCCT study)[490] was applied (not the first year effect). This was changed in a sensitivity analysis where no annual progression was assumed.

Intensive glycaemic control based on the DCCT study was selected as opposed to standard glycaemic control which determined the transition probabilities.

Baseline event rates

The cohort baseline HbA1c level was based on the National Diabetes Audit data for UK adult population with type 1 diabetes (9.3%).[18]

The baseline hypoglycaemic event rate in the base case was 110/100 patient years for major hypos and 3550/100 patient years for minor hypos, based on the UK Hypoglycaemia Study Group.[16] For patients with hypo unawareness this rate is six-fold[160] and it was used in a sensitivity analysis which takes into account this specific population. In the base case the same baseline event rate was used for all the strategies as we did not have data specific to the interventions compared, however we vary this in a sensitivity analysis where CGM was assumed to reduce the number of hypoglycaemic events.

Relative treatment effects

The main clinical outcome used in the model is the change in HbA1c level which then influences the downstream events as defined in the CORE model. Strategy-specific HbA1c reductions were obtained from the clinical literature (see Chapter 9 in the Full Guideline): the study by Miller et al (2013)[331] was used to compare SMBG frequencies as this cross-sectional study was the only one to report frequencies of SMBG that were selected for comparison in the model; for the effectiveness of CGM at reducing HbA1c the meta-analysis conducted for our clinical review and reported in Chapter 9, using the real-time CGM data only . One of the studies included in the meta-analysis[296] was retrieved in the updated search at the end of the guideline and could not be included in the model, however

the difference in HbA1c in the meta-analysis with or without the latest study was considered to be negligible (-0.34% without versus -0.30% with the study). The frequency of SMBG against which CGM was compared in the clinical studies was uncertain and therefore an assumption had been made that this was 4 times per day in the base case; this was varied in a sensitivity analysis where the reduction in HbA1c was assumed to be estimated versus a higher frequency of 10 per day (best case scenario for CGM).

The overall effectiveness estimates are reported in the table below together with the annual cost of the interventions.

Table 97: Effectiveness data associated with the strategies in the model

Intervention	Average HbA1c	Average Hba1c change versus SMBG	Average HbA1c change from baseline[(a)]
SMBG 2	9.11		-0.19
SMBG 4	8.24		-1.06
SMBG 6	7.74		-1.56
SMBG 8	7.43		-1.87
SMBG 10	7.21		-2.09
CGM	NR	-0.34	- 1.4 (b)

(a) HbA1c baseline was obtained by the National Diabetes Audit and was 9.3%
(b) In the base case this was estimated as the sum of the two changes: CGM versus SMBG (-0.34) and SMBG 4 times versus baseline (-1.06).

Hypoglycaemic event rates were not obtained from our clinical data as they showed counter-intuitive results (the higher the frequency of SMBG testing, the higher the hypoglycaemic events); this was explained by the bias inherent in cross-sectional studies where patients who are more at risk of hypoglycaemic events are more likely to test more frequently (there is an inverse relationship between cause and effect). We have kept the event rates constant for every strategy but we have changed this in a sensitivity analysis.

No data was found specifically on the quality of life associated with different strategies.

Resource use and costs

The interventions costs reflected the frequency of monitoring with SMBG and the cost of the CGM monitors. Glucose monitors for SMBG are usually provided for free by the manufacturer; the costs of SMBG strategies were estimated by multiplying the daily frequencyof monitoring by the unit cost of strips and lancets (£0.25 and £0.04 respectively), which were obtained from the average of the unit cost of all the strips and lancets reported in the NHS Drug Tariff, November 2014.[369] The total annual cost thus calculated is reported in Table 98.

Table 98: Cost data associated with the strategies in the model

Intervention	Annual cost
SMBG 2	£212
SMBG 4	£423
SMBG 6	£635
SMBG 8	£847
SMBG 10	£1,059
CGM	£3,511

The cost of CGM strategy was based on the average of three of the main technologies available in the UK: Dexcom G4, Abbott Freestyle, and Medtronic RT Guardian. The items included in the estimation of the annual cost were the receiver, sensors, transmitters, and calibration (self-blood tests). Details are reported in Table 99.

Table 99: Cost of CGM strategy

Intervention	Item	Unit cost	Units per year	Annual cost
Dexcom G4	Receiver	£1750	1/5	£374 (a)
	Sensors	£250/4	52	£3,250
	Transmitters	£275	2	£550
	Calibration	£0.29	2*365 (b)	£212
	Total			**£4,392**
Abbott Freestyle	Receiver	£950	1/5	£203 (a)
	Sensors	£288/6	60	£2,880
	Transmitters	Na (c)	0	0
	Calibration	£0.29	1*365 (d)	£106
	Total			**£3,189**
Medtronic RT Guardian	Receiver	£1,059(e)	1/5	£227 (a)
	Sensors	£420/10	60	£2,520
	Transmitters	£490 (f)	1(f)	£490
	Calibration	£0.29	2*365 (b)	£212
	Total			**£2,965**
			Total average cost (first year)	**£3,511**
			Total average cost (second year and after)	**£3,674**

(a) Annual cost estimated assuming a five year life span and a discount (dis) of 3.5% using the formula: purchase cost/(1-1/(1+dis)^(life span -1))/dis)
(b) Assuming SMBG for calibration is performed twice a day
(c) Rechargeable
(d) On average calibration is performed once per day
(e) Total initial cost of £1,599 included also the cost of sensors, which has been subtracted by the initial cost.
(f) Except for the first year.

No other differences in costs were assumed between strategies.

P.2.3 Computations

See Appendix N – paragraph N.2.3.

P.2.4 Sensitivity analyses

A number of sensitivity analyses were undertaken to test the robustness of the model results. The assumption used in SA1 was then used throughout the other SA performed.

SA1: Comparator for effectiveness of CGM

The improvement in HbA1c level is assumed to be estimated compared to SMBG 4 times in the base case (conservative assumption). In a SA we assume the same effectiveness of CGM was estimated against SMBG 10 times, therefore CGM is overall more effective in this sensitivity analysis. The overall reduction in HbA1c from baseline is estimated as the reduction of CGM versus SMBG (-0.34)

plus the reduction of SMBG 10 times versus baseline (-2.09), giving a total reduction from baseline of-2.43.

SA2: HbA1c progression (in combination with SA1)

In the base case analysis, the CORE model default value for the annual progression in HbA1c was used (0.045%). An alternative assumption of no annual progression in HbA1c level (0%) was tested. Based on the GDG clinical experience, HbA1c levels in type 1 diabetes patients tend to be stable, unlike the case in type 2 diabetes patients.

SA3: Utility estimation method (in combination with SA1)

In the base case analysis, the CORE model default "minimum approach" to calculating utility was used. In this approach, the quality of life for patient with multiple complications is assumed to take the minimum of the utility values associated with these complications. An alternative "multiplicative approach" was tested whereby utility for these patients is calculated as a multiplicative function of the utilities for these complications.

SA4: Discounting (in combination with SA1)

We used a discount rate of 1.5% for both costs and benefits.

SA5: Rate of severe/major hypoglycaemic events in hypo unaware population (in combination with SA1)

In the base case analysis, we did not take into account the possible difference between strategies in the rates of major hypoglycaemic events. However the GDG believed one of the main benefits of CGM is the decrease in the number of hypoglycaemic events, especially on a population with hypoglycaemia awareness problems. In this SA, the baseline rate of hypoglycaemic events was 6 times higher (660 per 100-patient years) than in the base case analysis in a general population, while the hypoglycaemic events rate in the CGM strategy was decreased up to 0 while it was kept constant (660 per 100-patient years) in the comparator.

SA6: Rate of severe/major hypoglycaemic events in hypo unaware population and cost of CGM (in combination with SA1)

This was the same as SA5 but in addition the cost of CGM was reduced to 70% of the base case cost as the GDG advised that self-testing could be less frequent than the twice a day assumption, and there could be some price reduction as well in the equipment cost.

SA7: Using a prevalent cohort (in combination with SA1)

In the base case analysis, the simulated cohort represented young adults (mean age 27 years). A SA was run assuming a cohort representing all type 1 diabetes population in the UK. Data for the cohort were obtained from the National Diabetes Audit[18] and are reported in the table below, compared to the base line data.

Table 100: Cohort characteristics in SA7 compared to the baseline values

Input variable	Baseline value	SA value
Patient demographics		
Start age (years)	27	43
Duration of diabetes (years)	9.10	17
Proportion Male	55.2%	56.7%

Input variable	Baseline value	SA value
Baseline risk factors		
HbA1c (-points)	9.3%	8.6%
Systolic Blood Pressure (mmHg)	121.48	128.27
Body mass index (BMI) (kg/m^2)	24.90	27.09
Proportion smoker	26%	22.35%

P.2.5 Model validation

The analysis was developed in consultation with the GDG; model inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

P.2.6 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:
- ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of two other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$

Where: λ = threshold (£20,000 per QALY gained)

Cost-effective if:
- Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

P.2.7 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[359] sets out the principles that GDGs should consider when judging whether an intervention offers good value for

money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several comparators, we use the NMB to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a cost-effectiveness threshold of £20,000 per QALY gained.

P.3 Results

P.3.1 Base case

The average cost and QALYs gained with each strategy are reported in Table 101. In this table interventions are ranked according to their mean net monetary benefit, which depends on the costs, QALYs and cost-effectiveness threshold (set at £20,000/QALY in our analysis).

Table 101: Base case probabilistic results in the model

Strategy	Discounted costs		Discounted QALYs		Net monetary benefit (£)	Rank by NMB
	Mean per patient (£)	SD (low – high 95% CI)	Mean per patient	SD (low – high 95% CI)		
SMBG 2	42,862	22,118 (41,491 – 44,233)	10.83	3.654 (10.606 – 11.059)	173,702	5
SMBG 4	43,027	21,302 (41,707 – 44,348)	11.43	3.575 (11.204 – 11.647)	185,272	4
SMBG 6	44,862	20,691 (43,579 – 46,144)	11.75	3.521 (11.527 – 11.963)	189,730	3
SMBG 8	47,478	20,511 (46,207 – 48,749)	11.93	3.481 (11.718 – 12.149)	190,766	1
SMBG 10	50,331	20,182 (49,080 – 51,582)	12.06	3.457 (11.843 – 12.271)	190,284	2
CGM	95,241	24,132 (93,745 – 96,737)	11.65	3.539 (11.427 – 11.865)	142,191	6

Overall, SMBG 8 times was ranked the most cost effective strategy in the base case analysis, however the ICER of SMBG 10 times compared to SMBG 8 times was just above the £20,000 per QALY gained threshold (£23,008/QALY). CGM is less effective and more costly than SMBG 8 and SMBG 10 when its effectiveness in terms of HbA1c reduction was assumed to be estimated compared to SMBG 4 times.

Table 15 presents the breakdown of the life-time costs per patient to the main cost categories (from the probabilistic analysis).

Table 102: Breakdown of life-time costs per patient by category

Strategy / Category	SMBG 2	SMBG 4	SMBG 6	SMBG 8	SMBG 10	CGM (assumed versus 4)
Intervention	3,283	6,857	10,519	14,208	17,906	60,318
Management	1,743	1,826	1,871	1,897	1,913	1,857
Hypoglycaemia	4,406	4,607	4,715	4,780	4,822	4,683
Complications						
Cardiovascular	3,117	3,024	2,972	2,946	2,893	2,988
Renal	12,355	10,023	8,783	8,104	7,665	9,195
Ulcer/Amputation/Neuropathy	10,880	10,027	9,618	9,312	9,052	9,703
Eye	5,938	5,510	5,230	5,074	4,927	5,345
Anti-Depression Treatment	1,141	1,153	1,154	1,155	1,153	1,154
Total Costs	42,862	43,027	44,862	47,478	50,331	95,241

The results of the deterministic analysis (**Error! Reference source not found.**) show that overall ALYs are higher than in the probabilistic sensitivity analysis and the more effective strategies are also more cost effective in the deterministic than in the probabilistic analysis. This explains why SMBG 10 times daily is the first ranking in terms of NMB in the deterministic analysis (the ICER is £15,184 per QALY, below the cost effectiveness threshold) while it is second in the probabilistic analysis (the ICER is £23,008, just above the threshold).

Table 103: Deterministic results (mean per patient)

Strategy	Costs[a]	QALYs[b]	NMB[c]	Rank[d]
SMBG 2	45,572	12.172	197,868	5
SMBG 4	43,573	12.847	213,367	4
SMBG 6	44,340	13.186	219,380	3
SMBG 8	46,627	13.439	222,153	2
SMBG 10	49,026	13.597	222,914	1
CGM	101,095	13.091	160,725	6

(a) Discounted life-time costs per patient
(b) Discounted life-time quality-adjusted life years (QALYs) per patient
(c) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(d) Ranked in descending order according to NMB

P.3.2 Sensitivity analyses

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The parameters and assumptions tested have been explained in P.2.4 while the results are reported in Table 104 below.

Table 104: Results of sensitivity analyses

	Most cost effective strategy in deterministic sensitivity analysis	Most cost effective strategy in probabilistic sensitivity analysis
SA1 – comparator for effectiveness of CGM	SMBG 10 times daily	SMBG 8 times daily
SA2 – HbA1c progression (+SA1)	SMBG 10 times daily	SMBG 8 times daily
SA3 – utility estimation method (+SA1)	SMBG 10 times daily	SMBG 10 times daily

	Most cost effective strategy in deterministic sensitivity analysis	Most cost effective strategy in probabilistic sensitivity analysis
SA4 – Discounting	SMBG 10 times daily	SMBG 10 times daily
SA5 – Rate of severe/major hypo events in population with hypo unawareness problems	SMBG 10 times daily across the whole range used	Only run deterministically
SA6 – SA5 + cost of CGM 70%	SMBG 10 times daily across the whole range used	Only run deterministically
SA7 – Prevalent cohort	SMBG 10 times daily	SMBG 10 times daily

Throughout these sensitivity analyses, when they were run deterministically SMBG 10 times daily remained always the most cost effective strategy, while CGM was always more effective but more costly than SMBG 10 times daily and the ICER was always above the £20,000 per QALY threshold. When the sensitivity analyses were run probabilistically, either SMBG 8 or 10 times daily was the optimal strategy according to the parameter that was changed, however CGM was never cost effective.

In the analysis conducted in a hypothetical cohort of patients with hypoglycaemia unawareness problems, CGM was still not cost effective and the ICER was £30,203 per QALY (deterministic analysis) even when the hypo events with CGM were 0 and the cost of CGM was 70% of the base case value.

P.4 Discussion

P.4.1 Summary of results

In the base case analysis SMBG 8 times daily was the optimal strategy at the £20,000 per QALY threshold. However SMBG 10 times daily was more effective and the ICER compared to SMBG 8 times daily was around £23,000 per QALY. When the model was run deterministically, the QALY increase with each strategy increased proportionally with the effectiveness (ie the more effective the higher the QALY increase compared to the probabilistic analysis) and in this analysis the ICER of SMBG 10 times daily went below the £20,000 per QALY threshold. In the sensitivity analyses that have been conducted either SMBG 8 or SMBG 10 times daily was the optimal strategy at the £20,000 per QALY threshold. CGM was never cost effective even when the conservative assumptions were changed (e.g. the decrease in HbA1c was assumed to have been estimated against SMBG 10 times instead of 4 times, or the total cost of CGM was decreased. The cost breakdown shows that CMG has a high intervention cost compared to SMBG and even in the sensitivity analysis where its effectiveness was increased, this did not justify the high cost.

P.4.2 Limitations and interpretation

This analysis was limited for a number of reasons: the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. Also the population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues, also because the price of CGM equipment is lower when used in conjuction with insulin pumps.

There is, inevitably, uncertainty around the model parameter inputs, however, the model results were tested in a wide range of sensitivity analyses which showed that the optimum choice (insulin

detemir twice daily) was the most cost effective at the £20,000 per QALY gained threshold. There was less certainty around the choice of the second and third best options, where insulin detemir once daily and insulin glargine once daily were both possible options.

This original economic analysis is based on many parameters that are not specific to a type 1 diabetes population but utilises data on the type 2 population as well. It also utilises reduction in HbA1c as one of two main clinical outcome measures which is an intermediate outcome measure; however this is considered to be a reliable proxy measure of disease progression and complications outcomes. Its link to the most important clinical outcomes for diabetes patients is already well established and validated.

Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, it was believed that the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.[104]

P.4.3 Generalisability to other populations or settings

This original economic analysis is directly applicable to the UK adult type 1 diabetes population. Generalisability of its findings to the paediatric type 1 diabetes population or populations or settings not included in the guideline scope is not appropriate.

Also, the population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues.

P.4.4 Comparisons with published studies

In the economic literature review, two economic evaluations were included that looked at CGM compared to SMBG.[226,325] Similarly to our analysis, they both concluded that CGM is not cost effective compared to SMBG.

P.4.5 Conclusions

The model showed that testing 8 or 10 times a day are the optimal strategies as they improved outcomes (reducing HbA1c level) at an acceptable cost compared to testing less frequently. The CGM strategy was never cost effective compared to SMBG 10 times even when its cost was decreased by 30% and the decrease in HbA1c was assumed to be calculated against SMBG 10. This is because of the high ongoing cost of CGM which is never offset by its effectiveness.

Appendix Q: Unit costs

Table 105: Insulin treatment

	Insulin	Vial	Unit Cost	Cartridges	Unit Cost
Short-acting insulin					
Insulin					
	Hypurin® Bovine Neutral	10 ml vial	£18.48	5 x 3 ml cartridges	£27.72
	Hypurin® Porcine Neutral	10 ml vial	£16.80	5 x 3 ml cartridges	£25.20
	Actrapid®	10 ml vial	£7.48		
	Humulin S®	10 ml vial	£15.68	5 x 3 ml cartridges	£19.80
	Insuman® Rapid			5 x 3 ml cartridges	£17.50
Insulin Aspart					
	NovoRapid®	10 ml vial	£16.28	5 x 3 ml cartridges	£28.31
				5 x 3 ml FlexPen prefilled	£30.60
				5 x 3 ml FlexTouch prefilled	£32.13
Insulin Glulisine					
	Apidra®	10 ml vial	£16.00	5 x 3 ml cartridges	£28.30
				5 x 3 ml SoloStar prefilled	£28.30
Insulin Lispro					
	Humalog®	10 ml vial	£16.61	5 x 3 ml cartridges	£28.31
				5 x 3 ml KwikPen prefilled	£29.46
Intermediate- and long-acting insulin					
Insulin Degludec					
	Tresiba®			5 x 3 ml cartrdiges	£72.00
				5 x 3 ml FlexPen prefilled	£72.00
				3 x 3 ml FlexPen prefilled (200IU)	£86.40
Insulin Detemir					
	Levemir®			5 x 3 ml cartrdiges	£42.00
				5 x 3 ml FlexPen prefilled	£42.00
				5 x 3 ml InnoLet prefilled	£44.85
Insulin Glarine					
	Lantus®	10 ml vial	£30.68	5 x 3 ml cartridges	£41.50
				5 x 3 ml SoloStar prefilled	£41.50
Insulin Zinc Suspension					
	Hypurin® Bovine Lente	10 ml vial	£27.72		
Isophane Insulin (NPH)					
	Hypurin® Bovine Isophane	10 ml vial	£27.72	5 x 3 ml cartridges	£41.58
	Hypurin® Porcine Isophane	10 ml vial	£25.20	5 x 3 ml cartridges	£37.80
	Insulatard®	10 ml vial	£7.48	5 x 3 ml cartridges	£22.90

	Insulin	Vial	Unit Cost	Cartridges	Unit Cost
				5 x 3 ml InnoLet prefilled	£20.40
	Humulin I®	10 ml vial	£15.68	5 x 3 ml cartridges	£19.08
				5 x 3 ml KwikPen prefilled	£21.70
	Insuman® Basal	5 ml vial	£5.61	5 x 3 ml cartridges	£17.50
				5 x 3 ml SoloStar prefilled	£19.80
Protamine Zinc Insulin					
	Hypurin® Bovine Protamine Zinc	10 ml vial	£27.72		
Biphasic (mixed) insulin					
Biphasic Insulin Aspart					
	NovoMix® 30			5 x 3 ml cartridges	£28.84
				5 x 3 ml FlexPen prefilled	£30.68
Biphasic Insulin Lispro					
	Humalog® Mix25	10 ml vial	£16.61	5 x 3 ml cartridges	£29.46
				5 x 3 ml KwikPen prefilled	£30.98
	Humalog® Mix50			5 x 3 ml cartridges	£29.46
				5 x 3 ml KwikPen prefilled	£30.98
Biphasic Isophane Insulin					
	Hypurin® Porcine 30/70 Mix	10 ml vial	£16.80	5 x 3 ml cartridges	£25.20
	Humulin M3®	10 ml vial	£15.68	5 x 3 ml cartridges	£19.08
				5 x 3 ml KwikPen prefilled	£21.70
	Insuman® Comb 15			5 x 3 ml cartridges	£17.50
	Insuman® Comb 25	5 ml vial	£5.61	5 x 3 ml cartridges	£17.50
				5 x 3 ml SoloStar prefilled	£19.80
	Insuman® Comb 50			5 x 3 ml cartridges	£17.50

Source: MIMS March 2013

Table 106: Needle Costs[a]

Needle length	4 mm	4.5 mm	5 mm	6 mm	8 mm	10 mm	12 mm
Cost per needle[b]	£0.11	£0.12	£0.14	£0.10	£0.10	£0.07	£0.08
Cost per day	£0.44	£0.49	£0.56	£0.41	£0.40	£0.30	£0.32
Cost per week	£3.05	£3.45	£3.89	£2.89	£2.82	£2.09	£2.26
Cost per month	£12.19	£13.80	£15.56	£11.57	£11.27	£8.35	£9.02
Cost per year	£158.87	£179.87	£202.81	£150.76	£146.95	£108.82	£117.60

(a) Assuming four injections a day with single use needles
(b) Average of all needles that length (MIMS October 2013)

Table 107: Unit costs for self-monitoring of ketones

Self-monitoring ketones	Usage	Cost	Quantity	Cost Per Unit	Reference
Ketostix	Urine Test	£3.00	50	£0.06	(a)
Mission Ketone	Urine Test	£2.50	50	£0.05	(a)
FreeStyle Optimum ß-Ketone Test Strips	Blood Test	£20.63	10	£2.06	(a)
Optimum Xceed	Monitor	Ask GDG	1	Free	(b)
GlucoMen LX Ketone Test Strips	Blood Test	£20.32	10	£2.03	(a)
GlucoMen LX	Monitor	Ask GDG	1	Free	(b)

(a) Electronic Drug Tariff – November 2012
(b) GDG opinion – Monitors are given away free by medical devices companies. Normal cost ranges around £10 to £15

Table 108: Unit costs for in-hospital ketone monitoring

In-hospital ketones	Usage	Cost	Quantity	Cost Per Unit	Reference
Biochemistry Blood Test	Blood Test	£1.26	1	£1.26	(a)
FreeStyle Optimum ß-Ketone Test Strips	Blood Test	£20.63	10	£2.06	(a)
GlucoMen LX Ketone Test Strips	Blood Test	£20.32	10	£2.03	(a)
Ketostix	Urine Test	£3.00	50	£0.06	(b)
Mission Ketone	Urine Test	£2.50	50	£0.05	(b)
Nurse time	Administer Test	£40 an hour	5 minutes	£3.33	(c)

(a) NHS Reference Cost – 2010/11
(b) Electronic Drug Tariff – November 2012
(c) PSSRU 2011[106] - 14.3 – Cost of a band 5 nurse on a standard day ward (+qualification cost)

Appendix R: Research recommendations

R.1 Improved methods and interventions for achieving HbA1c targets in adults with type 1 diabetes

Research question: In adults with type 1 diabetes, what methods/interventions can be used to increase the number who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

Why this is important:

The evidence that sustained near-normoglycaemia substantially reduces risk of long-term complications in adults with type 1 diabetes is unequivocal. Current methods for achieving such glycaemic control require skills in glucose monitoring and insulin dose adjustment, injection technique and site management, and the ability to use such self-management skills on a day-to-day basis life-long. Fears of hypoglycaemia and weight gain are major barriers to success, as is fitting diabetes self-management into busy lifestyles. Everyone struggles to meet optimised targets and some are more successful in achieving them than others. Research into new interventions ranging from more effective education and support, through improved technologies in terms of insulin replacement and glucose monitoring, and including use of cell-based therapies, are urgently needed. It is also important to ensure that adults with type 1 diabetes are able to engage with such methodologies

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults with type 1 diabetes. **Intervention:** technologies, education, support **Comparison:** usual care (glucose monitoring and insulin dose-adjustment) **Outcomes:** • HbA1c change • Percentage of patients reaching target HbA1c value • Hypoglycaemia (number of episodes and number of patients experiencing an episode) • Severe hypoglycaemia (number of episodes and number of patients experiencing an episode) • Nocturnal hypoglycaemia (number of episodes and number of patients experiencing an episode) • Weight change • Fear of hypoglycaemia • QoL measures (diabetes specific) • Cost-effectiveness outcomes eg. EQ-5D
Importance to patients or the population	Adults with type 1 diabetes are made aware of the importance of achieving glucose and HbA1c targets but the day-to-day management of their insulin regimens requires skills and concentration. Current management still requires estimation of insulin requirement with every administration and continues to carry risk of error. Fear of such error and of the apparently unpredictable responses to insulin, are a problem for people with diabetes and interfere with their ability to achieve optimal outcomes. We therefore require new methods that can more easily engage all adults with type 1 diabetes in achieving optimal outcomes. Improved glycaemic control has the potential to reduce acute complications of therapy such as hypoglycaemia, diabetic ketoacidosis and

	weight gain, and risk of long term complications, with significant personal and economic benefit. Four of the top 10 research priorities are addressed in this one overarching research question (is insulin pump therapy effective [immediate vs. deferred pump], and comparing outcomes with multiple injections; is an artificial pancreas for Type 1 diabetes (closed loop system) effective; does treatment of adults with type 1 diabetes by specialists (e.g. doctors, nurses, dieticians, podiatrists, ophthalmologists and psychologists) trained in person-centred skills provide better blood glucose control, patient satisfaction and self-confidence in the management of Type 1 diabetes, compared with treatment by non-specialists with standard skills; what makes self-management successful for some people with Type 1 diabetes, and not others?) although the present question is framed to address how to increase access to existing best practice as well as implying the need to develop improved systems.
Relevance to NICE guidance	The guideline describes evidence-based best practice, but recognises that even current best practice does not achieve optimal outcomes; with many adults with type 1 diabetes not achieving targets, and others troubled by side effects. The guideline covers some strategies to reduce risks of hypoglycaemia and of weight gain associated with insulin therapy but recognises the need for further development of the technologies and strategies used to engage and support adults with type 1 diabetes to achieve and maintain optimal control.
Relevance to the NHS	Treating the acute and chronic complications of type 1 diabetes is costly. Developing better ways to help adults with type 1 diabetes optimise their glucose control to minimise risk of complications and with minimal risk of side effects from their therapy (including the demands these therapies make upon them) will help reduce these costs.
National priorities	Adults with type 1 diabetes are typically working age and it is important to support them to perform and achieve at the level of their non-diabetic peers.
Current evidence base	The present evidence base shows the long term benefits in both physical and mental health for adults with type 1 diabetes, with reduced risk of long term complications seen in the follow up of the RCT of intensified insulin therapy in type 1 diabetes, the DCCT. While structured education programmes transferring skills of insulin dose adjustment form the health care professional to the user show an ability to lower HbA1c and lower hypoglycaemia and DKA risk, the DAFNE audits show inconsistent achievement of targets across centres and a mean HbA1c achieved that is still above target. Even addition of new technologies of insulin delivery and glucose monitoring do not allow every adult with diabetes to achieve and maintain glycaemic targets. On line glucose monitoring, for example, only provides benefit if used continuously, and a recent meta-analysis of insulin pump studies suggested very minor improvements in control. Further research into better therapies is still required.
Equality	There are concerns that access to structured education and use of new technologies of insulin delivery and glucose monitoring may be less available to people with literacy and numeracy issues or other emotional or sociological barriers to accessing best practice and these barriers should be investigated and addressed as part of the research effort to achieve better outcomes for all.
Study design	Randomised controlled trials of new interventions which might include new educational strategies; development of new insulins or insulin delivery systems; new glucose monitoring systems; supplementary therapies and novel interventions such as closed loop insulin delivery systems and cell based therapies.

Feasibility	Trials will be feasible. There are no ethical or technical issues.
Other comments	None
Importance	High. This research is essential further to improve outcomes for adults with type 1 diabetes.

R.2 Continuous glucose monitoring

Research question: In adults with type 1 diabetes who are chronically poorly-controlled, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

Why this is important:

Current CGM systems were found not to be cost-effective in our de-novo analysis, even in patients who had impaired awareness of hypoglycaemia. In patients who are poorly controlled, there still may be some value for using CGM systems, and therefore further research is needed to determine whether newer technologies would prove to be cost-effective, particularly in these patients.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults with type 1 diabetes with chronically poorly controlled blood glucose. **Intervention:** continuous glucose monitoring technologies **Comparison:** SMBG, current CGM technologies **Outcomes:** • HbA1c change • Hypoglycaemia (number of episodes and number of patients experiencing an episode) • Severe hypoglycaemia (number of episodes and number of patients experiencing an episode) • Nocturnal hypoglycaemia (number of episodes and number of patients experiencing an episode) • Fear of hypoglycaemia • QoL measures (diabetes specific) • Cost-effectiveness outcomes eg. EQ-5D
Importance to patients or the population	Current practice for self-monitoring and adjustment of insulin doses requires a finger prick blood sample and meter measurement of the plasma glucose, with our evidence review suggesting 4 – 10 tests a day are associated with benefit, but testing is mildly traumatic and inconvenient. Continuous monitoring of an approximation of plasma glucose in real time is a relatively new development. The advent of such systems, which can provide a continuous visual read-out of plasma glucose has been would seem to have obvious potential benefit, allowing people to know what their blood glucose is at any moment, and most particularly (because there is a time lag between the measurement of interstitial plasma glucose and the real plasma glucose which varies according to rate of change), showing direction and speed of change, thus providing warning of extremes of hypo- or hyper-glycaemia. The literature to date shows a modest overall reduction in CGM but this was not a cost-effective benefit. There was benefit in reducing severe hypoglycaemia. There are however also strong data to show that benefit required strong commitment to the technology and near-constant use. Although a patient-level meta-analysis has suggested greater benefit in people with higher starting Hba1, there are no robust data to show benefit in adults with type 1 diabetes struggling with long term high HbA1c, in whom a reduction towards target would have significant potential health and economic benefits .

Relevance to NICE guidance	The guideline is recommending a near-normal glycated haemoglobin target for adults with type 1 diabetes as a means of reducing long term complications and ill health. Technologies to help people achieve this target more safely and with fewer side effects are therefore relevant.
Relevance to the NHS	The CGM systems are attractive to adults with type 1 diabetes but costly. It is essential to define their place in helping adults with type 1 diabetes achieve improved glycaemic targets, so that the technology is deployed most rapidly to the people who stand to benefit in a cost effective manner.
National priorities	N/A
Current evidence base	12 studies found an overall reduction in HbA1c of 0.3%, when CGM was compared with regimented and frequent SMBG, and without an increase in hypoglycaemia, which the GDG considered clinically useful, but a greater improvement would need to be more for people with high starting HBA1c.
Equality	Defining the people who can benefit most from the technology, irrespective of other issues, will determine the people for whom the NHS should support the new, relatively costly technology.
Study design	Randomised controlled trial of addition of CGM to otherwise protocolised care of type 1 diabetes.
Feasibility	A trial is feasible. There are no ethical or technical issues.
Other comments	None
Importance	High. This research is important to determine the cost-effective deployment of the technology in the NHS.

R.3 Structured education programmes

Research question: In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining glycaemic control targets)?

Why this is important:

Structured education programmes in flexible insulin therapy have been shown to improve diabetes control (lower HbA1c and less hypoglycaemia) but achieving and sustaining optimal diabetes control for avoidance of complications remains challenging. Some people fail to achieve ideal targets for glycaemic control; others achieve but cannot maintain them and still others do not access structured education at all. We therefore need to develop and test (1) more effective ways of engaging adults with type 1 diabetes in education; (2) improvements in the delivery of education to increase the number of people achieving targets for diabetic control and (3) enhanced support for adults with diabetes to sustain good diabetic control over time. If we can improve the uptake and delivery of clinically and cost effective education and support for adults with type 1 diabetes we will see a reduction in the short and long term complications of the condition.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults with type 1 diabetes **Intervention:** methods to improve uptake of structured education programmes (eg. methods of delivery, enhanced support) **Comparison:** Current structured education methods

	Outcomes: • HbA1c change • Percentage of patients attending structured education programme • Hypoglycaemia (number of episodes and number of patients experiencing an episode) • Severe hypoglycaemia (number of episodes and number of patients experiencing an episode) • Nocturnal hypoglycaemia (number of episodes and number of patients experiencing an episode) • QoL measures (diabetes specific) • Patient views • Cost-effectiveness outcomes eg. EQ-5D
Importance to patients or the population	Transferring skills of insulin dose adjustment to adults with type 1 diabetes has been shown to produce significant improvement in glycated haemoglobin, risk of severe hypoglycaemia, awareness of hypoglycaemia, rates of diabetic ketoacidosis and quality of life. Yet many adults with type 1 diabetes do not access properly constructed, quality controlled structured education, with some areas having long waiting lists or only able to offer unproven lighter versions of tested curricula. Some adult with type 1 diabetes may consider themselves ineligible for structured education, perhaps because they don't see the need, are unwilling to take the time or feel they lack literary or numeracy skills. Importantly health care professionals may also deem some adults with type 1 diabetes not to need, or to be unable to access, structured education. Finally, not all adults with type 1 diabetes achieve, or sustain, glycaemic targets after existing structured education. Identifying barriers to and increasing the effectiveness of current packages of structured education, and providing evidence based effective support for sustaining beneficial outcomes are key targets for provision of type 1 diabetes care. This question was included in the top 10 research priorities from the James Lind Alliance exercise, where it was framed as "What are the characteristics of the best type 1 diabetes patient education programmes (from diagnosis to long-term care) and do they improve outcomes?" A further included priority which is also addressed by the present question was "What makes self-management successful for some people with Type 1 diabetes, and not others?"
Relevance to NICE guidance	The GDG guideline recommends the very few structured education programmes for which there is an evidence base. Even at best, not all adults with type 1 diabetes access these programmes, and not all attendees achieve target glucose control or sustain it over time.
Relevance to the NHS	The GDG found very few evidence based English programmes in structured education, yet the NHS is spending significantly on unproven education packages. Devising and delivering an effective programme with ability to achieve glucose targets for a majority of adults with type 1 diabetes over years would result in significant benefit in terms of improved glycaemic control with reduced risk of chronic complications, reduced use of unscheduled care and reduced rates of anxiety and depression, all of which have been demonstrated by the DAFNE programme, but with limited data on ability to achieve benefit for all adults with type 1 diabetes and to sustain good outcomes over years
National priorities	N/A
Current evidence base	There is robust evidence for only one current English language programme to deliver reduced HbA1c and risk of severe hypoglycaemia, despite a multiplicity of packages in use.
Equality	This research may include, although not be limited to, addressing concerns,

	which need to be substantiated, that DAFNE may be less accessible to adults with type 1 diabetes who are not confident of their numeracy or literacy skills.
Study design	Qualitative and mixed methods studies to identify barriers to attending DAFNE, the course recommended by this guideline, to seek insight into how education programmes could be improved to enhance attendance, engagement and long term implementation of the principles taught, and randomised controlled trials and audited roll out of modified education packages
Feasibility	A trial is feasible. There are no ethical or technical issues.
Other comments	None
Importance	High. This research is essential to improve the outcomes of current management of all adults with type 1 diabetes .

R.4 Risk stratification tool for HbA1c targets

Research question: In adults with type 1 diabetes, can a risk stratification tool be used to aid the setting of individualised HbA1c targets?

Why this is important:

Strict glycaemic control early in the history of type 1 diabetes has been shown to reduce the development and progression of long term complications but we are unable to determine who is at particular risk of glucose-driven poor outcomes. Furthermore, there is a dearth of evidence of the risk:benefit ratio of strict glycaemic control in people who already have diabetes complications. As achieving and maintaining near-normal plasma glucose concentrations is complicated, a risk stratification tool to calculate the modifiable individual risk of complications will allow us to tailor glycaemic targets for each individual and provide appropriate support.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** Adults with type 1 diabetes (including those who already have complications) **Intervention:** risk stratification tool **Comparison:** No tool used (usual care / methods of HbA1c target setting) **Outcomes:** • HbA1c change • Percentage of patients achieving target HbA1c level • Hypoglycaemia (number of episodes and number of patients experiencing an episode) • Severe hypoglycaemia (number of episodes and number of patients experiencing an episode) • Nocturnal hypoglycaemia (number of episodes and number of patients experiencing an episode) • QoL measures (diabetes specific) • Cost-effectiveness outcomes eg. EQ-5D
Importance to patients or the population	Adults with type 1 diabetes are currently asked to achieve near-normal glucose control as often as possible, with good evidence linking intensive diabetes

	management to lower rates of diabetic complications. There are however no good data on the optimal target for people with existing complications, or who struggle with hypoglycaemia in their attempts to achieve good glycaemic control. Many adults with type 1 diabetes have lived with the condition for many decades and their need to achieve currently recommended glycaemic targets is not clear. Evidence from the literature in adults with advanced type 2 diabetes suggests that sustained unsuccessful attempts to normalise glycaemic control may even be deleterious in some and understanding whether or where this applies to the population of adults with type 1 is very important The James Lind Alliance exercise did not specifically list creating a risk stratification tool in its top 10 priorities, although the question "How tightly controlled do fluctuations in blood glucose levels need to be to reduce the risk of developing complications in people with type 1 diabetes?" is pertinent .
Relevance to NICE guidance	The guideline recommends a target HbA1c of ≤48 mmol/mol (≤6.5%)for all adults with type 1 diabetes, and although it recognises that this target may not be equally cost effective for everyone, ther are no data to indicate who these people are and what targets would be appropriate for them.
Relevance to the NHS	Identifying those adults with type 1 diabetes for whom less stringent targets may be appropriate will allow appropriate focussing of resources, and may be able to reduce pressure on individuals that produces limited benefit
National priorities	N/A
Current evidence base	The current evidence for a target HbA1c even lower than the present recommendation (≤6.05%) has long term benefit in terms of reduced risk of complications is strong but the RCT data come from people with no or early evidence of complications and disease duration less than 15 years. Understanding the need for such targets in people with longer duration type 1 diabetes and/or existing advanced complications will be beneficial.
Equality	This research recommendation does not address an equality issue.
Study design	Randomised controlled trial of adults with type 1 diabetes and established complications, such as laser treated retinopathy; modestly impaired renal function; a history of a cardiovascular event into a trial of 2 different HbA1c targets e.f (6 – 7% vs 7 – 8% with great care taken to avoid hypoglycaemia and mortality as one outcome measure
Feasibility	A trial is feasible but very strict protocols for achieving targets and monitoring of potential side effects such as weight gain and hypoglycaemia would be required
Other comments	None
Importance	High. We currently have no evidence on which to base advice on glycaemic targets for adults with long duration type 1 diabetes, with or without complications.

R.5 Technologies for prevention and treatment of hypoglycaemia unawareness

Research question: In adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or CGM, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for the prevention and treatment of hypoglycaemia unawareness?

Why this is important:

Impaired awareness of hypoglycaemia renders adults with type 1 diabetes susceptible to sudden unexpected deteriorations of conscious level and irrational behaviour, and increases risk of severe hypoglycaemia six-fold. Impaired awareness of hypoglycaemia and severe hypoglycaemia creates barriers to many aspects of daily living, and can cause enormous stress within family and friends. Severe hypoglycaemia can also cause fear of hypoglycaemia great enough to prevent a person achieving the glucose targets that are associated with minimal risk of complications. Impaired awareness of hypoglycaemia results from over-exposure to hypoglycaemia in daily life and awareness can be much improved by avoidance of hypoglycaemia.

Developing technologies in glucose monitoring and insulin delivery have not been rigorously tested in adults with type 1 diabetes and impaired awareness of hypoglycaemia. Research is needed formally to document the extent to which existing technologies can help the adult with type 1 diabetes and impaired awareness of hypoglycaemia avoid hypoglycaemic episodes and regain awareness for occasional episodes and research is also needed to develop new ones. Given evidence for reduced ability to engage with attempts to avoid hypoglycaemia in future in people with impaired awareness, research is also needed into how to engage adults with type 1 diabetes and impaired hypoglycaemia awareness with treatment strategies designed to improve awareness.

Criteria for selecting high-priority research recommendations:

PICO question	**Population:** a) Adults with type 1 diabetes. b) Adults with type 1 diabetes and impaired hypoglycaemia awareness **Intervention:** technologies (such as insulin pump therapy and/or CGM, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions **Comparison:** Current technologies, usual care **Outcomes:** • HbA1c change • Percentage of patients with impaired hypoglycaemia awareness • Gold or Clarke score • Hypoglycaemia (number of episodes and number of patients experiencing an episode) • Severe hypoglycaemia (number of episodes and number of patients experiencing an episode) • Nocturnal hypoglycaemia (number of episodes and number of patients experiencing an episode) • QoL measures (diabetes specific) • Cost-effectiveness outcomes eg. EQ-5D
Importance to patients or the population	Impaired awareness of hypoglycaemia increases the risk of severe hypoglycaemia in an adult with type 1 diabetes six-fold. The consequences of an episode of severe hypoglycaemia, resulting in transient loss of cognitive function, can be physically dangerous, embarrassing and socially problematic, with outcomes including physical injury, impaired work performance, inappropriate and sometimes violent behaviour to children and families and fear of hypoglycaemia, which is a major barrier not just to achieving good glycaemic control, as is often stated, but also to good quality of life for some adults with type 1 diabetes and their families. Some adults with type 1 diabetes have recurrent problems with impaired hypoglycaemia awareness and recurrent severe hypoglycaemia and this creates many problems for these people and their families. There is a belief in adults with type 1 diabetes and their health care professionals that there are no solutions for their problems, which may continue unchecked for years. There is evidence that adults with type 1 diabetes and impaired hypoglycaemia awareness may have difficulty in engaging with strategies to avoid hypoglycaemia, as their lack of awareness includes an

	unawareness of the severity of their problem. Recent data even suggest adults with type 1 diabetes are now failing to report severe hypoglycaemia, since the introduction of rigorous limits on hypoglycaemia in the assessment of fitness to hold a licence to drive. This creates a further barrier to adults with type 1 diabetes accessing treatment. The structured education programmes, with or without additional intensive health care professional support, restore awareness to many people with impaired awareness of hypoglycaemia. However, audit suggests about 30% of adults with type 1 diabetes have impaired awareness of hypoglycaemia one year after completing courses and there have been no RCTs of interventions for people whose hypoglycaemia problems persist after such education has been completed. Use of technologies such as adding CGM to insulin pump therapy, while it has been shown to reduce risk of severe hypoglycaemia, has not to date improved the endogenous defence of restored hypoglycaemia awareness. Cell therapies, such as islet and whole organ pancreas transplantation can protect against severe hypoglycaemia, with no formal studies of the impact on awareness. There is emerging evidence that psychological therapies can help restore awareness but this needs confirmation. it is not clear whether this is independent of restoration of behaviour change around self-management of hypoglycaemia risk. Research into ways of improving awareness of and preventing hypoglycaemia were in the top 10 research priorities of the James Lind Alliance assessment.
Relevance to NICE guidance	Hypoglycaemia is a risk of insulin therapy and fear of hypoglycaemia, both in adults with type 1 diabetes and their health care professionals, can limit the ability to achieve NICE targets
Relevance to the NHS	Emergency calls for severe hypoglycaemia are estimated to cost £13.6 m per annum in England alone. At least 50% of these episodes are likely to be people with type 1 diabetes. This costing does not include costs of self-treated episodes and economic costs related to lost work opportunities and restricted life options for adults with type 1 diabetes experiencing hypoglycaemia
National priorities	N/A
Current evidence base	There is evidence for benefit of several structured education programmes, with (eg HypoCompass) or without (eg DAFNE, BGAT) on-going intensive input from health care professionals. There is evidence for newer technologies (ispumps, sensors and islet replacement therapies) for reducing severe hypoglycaemia but not for impacting on awareness of hypoglycaemia. There are pilot data only to show benefit from psychological interventions using cognitive behavioural therapy and motivational enhancement.
Equality	This research recommendation does not address an equality issue.
Study design	Development and randomised controlled trial of new interventions including robust assessment of hypoglycaemia awareness and experience in adults with type 1 diabetes and impaired awareness of hypoglycaemia .
Feasibility	A trial is feasible. A potential difficulty is the increasing reluctance of adults with type 1 diabetes to disclose problematic hypoglycaemia.
Other comments	None
Importance	High. This research is essential. Unless new evidence is gained, we cannot complete

	a clear pathway of support for adults with type 1 diabetes who experience problems with hypoglycaemia.

Appendix S: Removed text from CG15

1 Preface (2004)

It is a pleasure to introduce this national guideline on Type 1 diabetes in adults, commissioned by the National Institute for Clinical Excellence (NICE) to identify best practice for the NHS in the management of Type 1 diabetes. It is the fourth such guideline to be prepared by the National Collaborating Centre for Chronic Conditions (NCC-CC) based at the Royal College of Physicians of London.

Type 1 diabetes can, if poorly controlled, produce devastating problems in both the short and the long term. Good control of blood glucose levels reduces the risk of these problems arising, but can be very difficult for patients and carers to achieve. This guideline emphasises that the NHS should provide all patients with the means – and the necessary understanding – to control their diabetes, and that it should help patients integrate the disease management with their other activities and goals. It argues that every person with diabetes should be able to develop their own care plan and utilise effective treatment in a way agreeable to them. The input of various health professionals may be needed to achieve this, and should be readily available. A system of regular monitoring, so that any complications which do develop are picked up at an early stage and treated appropriately, should also be provided.

In common with all NICE guideline recommendations, those for Type 1 diabetes have been developed using a rigorous, evidence-based methodology. An extensive search identified the relevant medical literature, and papers were carefully assessed to ensure that recommendations were based on treatment and practice of proven benefit. This process was carried out by a guideline development group (GDG), a small team from the NCC-CC working together with patients and health professionals with wide expertise in Type 1 diabetes. They have used the available evidence to produce guidance that is clinically relevant as well as methodologically sound. The availability of clinical expertise also allowed recommendations to be made in areas for which there is inadequate evidence, but which are important to patients and carers. At the same time the need for further research in these areas was indentified.

It goes without saying that the members of the GDG deserve enormous thanks for their efforts. The technical team at the NCC-CC, the GDG Lead, the Clinical Advisor and the rest of the group have all worked incredibly hard over the past two years, and have been most generous with their time. Thanks are also due to all those who commented on the guideline at various stages of development. Since I have assumed the directorship of the NCC-CC only at the very end of this process, I can say without any self-aggrandisement that they have done a magnificent job. This full guideline is both an excellent clinical reference work and a practical working document which will improve the care of those with Type 1 diabetes.

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Director, National Collaborating Centre for Chronic Conditions

3 Diagnosis [2004 content]

3.1 Rationale

The diagnosis of type 1 diabetes would not appear to present any problems once thought of, as a lifelong condition requiring treatment with a therapy of considerable health and social impact (insulin injections) it is important the diagnosis is secure. Additionally considerations arise over differentiation of types of diabetes.

3.2 Evidence

Diagnosis, in regard of types of diabetes, is generally not addressed by the WHO report 8.[527] That report notes that children present with severe symptoms, and the diagnosis is simply confirmed by blood glucose measurement (advice that may be regarded as dated).

WHO otherwise concentrates mainly on the situation pertaining to type 2 diabetes, in doing so noting (by reference to the 1985 report) the lack of need for challenge testing when plasma glucose levels are high, in the absence of other metabolic stress, and when confirmed by a second laboratory measurement or classic symptoms.

3.3 Comment

Type 1 diabetes is, for the most part, easily recognised and diagnosed, requiring hyperglycaemia to a significant degree (risk of microvascular complications), and islet B-cell destruction which may be detected as pathogenetic markers or poor insulin secretion.

Where the diagnosis of diabetes is equivocal, and hyperglycaemia is by definition marginal, management will follow generally guidelines for type 2 diabetes. In some such patients with 'type 2 diabetes' or diabetes of uncertain type, management will be by clinical stage even if autoimmune markers of type 1 diabetes are detected.

If type 1 diabetes is suspected, referral should be more urgent than with most other types of diabetes diagnosed in adults.

3.4 Consideration

The Group endorsed the commentary discussed above, and concluded that simple recommendations were all that were required. Although in this condition diagnosis of diabetes is rarely in doubt, errors do arise in attribution of diabetes type on occasions, and this is known to result in negative consequences including failure to anticipate ketoacidosis, or unnecessary insulin therapy. Accordingly the group felt that cautionary recommendations were in order. The group noted that formal evidence of the utility of tests to distinguish type of diabetes by autoimmune markers or measures of islet B-cell function was not positive, and that these tests were not routinely performed.

The group were keen to reiterate the importance of laboratory glucose estimation in line with WHO recommendations to avoid the very rare misdiagnoses with lifelong consequences. The role of symptoms and of HbA1c estimation were seen as useful but only supportive, as both lack absolute specificity.

3.5 Recommendations

1. **Diabetes should be confirmed by a single diagnostic laboratory glucose measurement in the presence of classical symptoms, or by a further laboratory glucose measurement. The diagnosis may be supported by a raised HbA1c. [2004]**

2. **Where diabetes is diagnosed, but type 2 diabetes suspected, the diagnosis of type 1 diabetes should be considered if:**
   - **ketonuria is detected, or**
   - **weight loss is marked, or**
   - **the person does not have features of the metabolic syndrome or other contributing illness. [2004]**

3. **When diabetes is diagnosed in a younger person, the possibility that the diabetes is not type 1 diabetes should be considered if they are obese or have a family history of diabetes, particularly if they are of non-white ethnicity. [2004]**

4. **Tests to detect specific auto-antibodies or to measure C-peptide deficiency should not be regularly used to confirm the diagnosis of type 1 diabetes. Their use should be considered if predicting the rate of decline of islet B-cell function would be useful in discriminating type 1 from type 2 diabetes. [2004]**

4 Care process and support [2004 content]

4.1.1 Recommendations

5. **Open access services should be provided on a walk-in and telephone-request basis during working hours to adults with Type 1 diabetes, and a helpline staffed by people with specific diabetes expertise should be provided on a 24-hour basis. Adults with diabetes should be provided with contact information for these services. (Grade C)**

6. **The multidisciplinary team approach should be available to inpatients with Type 1 diabetes, regardless of the reason for admission (see section 13.3, 'Inpatient management'). (Grade D)**

5 Education programmes and self-care

5.1 Education programmes for adults with Type 1 diabetes

5.1.1 Evidence statements

Content of education

There were no trials located in newly diagnosed people with Type 1 diabetes specifically, or concerned with the initial content of education. The American Diabetes Association guidelines suggest that as part of initial visit people should be referred to a diabetes educator if education is not provided by the physician or practice staff, but content of this education is not defined **(IV)**.[32]

Educational setting

One small randomised controlled trial comparing the efficacy of classroom teaching of diabetes skills, compared to individualised learning, found that classroom teaching led to a greater level of awareness about diabetes self-care.[77] However, there was no significant difference in terms of the level of use of self-care practices. Furthermore, the two education techniques provided no different outcome of levels of technical skill in self-care. However this study made no analysis of comparability of study groups at baseline and was not blinded (**Ib**).

Technology interventions

One randomised controlled study compared two interactive computer schemes to reinforce an educational video. The first gave additional feedback and information on the correct answers, the second only the correct answers.[252] People with diabetes in the interactive group scored significantly better in a follow-up test of diabetes knowledge than those following the standard scheme. There were no significant differences in user ratings for the two software packages, but the people in the additional feedback group had a better diabetes knowledge at baseline, so the results may be biased by this confounding factor **(Ib)**.

Guidelines for self-management education

An update of the US standards for diabetes self-care management based on a literature review covered the organisation of diabetes self-management education, its content and provision.[328] A multiprofessional task force encompassing all the major interested stakeholders agreed the following standards **(IV)**.

- Education and information-giving will involve the interaction of the individual with diabetes with a multifaceted education instructional team, which may include a behaviourist, exercise physiologist, ophthalmologist, optometrist, pharmacist, physician, podiatrist, registered dietitian, registered nurse, other healthcare professionals, and paraprofessionals.
- Instructors will obtain regular continuing education in the areas of diabetes management, behavioural interventions, teaching and learning skills, and counselling skills.
- Assessed needs of the individual will determine which content areas listed below are delivered:

  - describing the diabetes disease process and treatment options
  - incorporating appropriate nutritional management
  - incorporating physical activity into lifestyle
  - utilising medications (if applicable) for therapeutic effectiveness
  - monitoring blood glucose, urine ketones (where appropriate) and using results to improve control
  - preventing, detecting, and treating acute complications
  - preventing (through risk reduction behaviour), detecting, and treating chronic complications
  - goal-setting to promote health, and problem-solving for daily living
  - integrating psychosocial adjustment to daily life
  - promoting preconception care, management during pregnancy, and gestational diabetes management (if applicable).
- An individualised assessment, development of an education plan and periodic reassessment between participant and instructor will direct the selection of appropriate educational materials and interventions.
- The assessment includes relevant medical history, cultural influences, health beliefs and attitudes, diabetes knowledge, self-management skills and behaviours, readiness to learn, cognitive ability, physical limitations, family support, and financial status.
- There shall be documentation of the individual's assessment, education plan, intervention, evaluation, and follow-up in the permanent confidential education record.

General education programmes

Within an overall review of patient education models for diabetes (not type-specific) one health technology appraisal reviewing four controlled trials of a range of education programmes including items of self-management, self-monitoring, diet, the effects of insulin and exercise, taught by a variety of staff or self-taught, and as an initial intense course or as ongoing programmes reported a variety of positive outcomes compared to normal care.[416] This review found that one study had demonstrated improvements over 10 years in diabetic control, in terms of reduced HbA_{1c} levels. In another study an intensive five-day training course was found to be effective in reducing HbA_{1c} levels. In one study there was no difference in blood glucose control with education compared to usual care, while there were no between-group comparisons made in another other study. Education was also shown to improve blood pressure. There is limited evidence to suggest a reduced rate of ketoacidosis and reduced hospitalisation. However, there was no evidence to indicate that education can reduce body mass index. There is some data to suggest increased incidence of hypoglycaemic episodes. Long-term outcomes of retinopathy, or neuropathy were not found to be significantly affected by education, but there is some limited evidence to suggest nephropathy incidence is improved, although rates were low. Unsurprisingly, diabetes knowledge was significantly improved with education, although this was not true of quality of life. Overall the included trials were of moderate methodological rigour. Three of the trials included were investigating education in the context of intensification of treatment compared to normal care, and it is difficult to be sure that the benefits reported are directly attributable to the education aspect of the intervention (**NICE**).

Metabolic control and quality of life were not found to be significantly affected by a structured outpatient programme of education led by a nurse, dietitian, and other people with diabetes over 4 weeks in a large randomised trial as compared to conventional care (**Ib**).[120]

A medium sized randomised controlled trial of a monthly education programme at which different aspects of diabetes treatment and technical skills were considered found that after one year of education HbA_{1c} levels were reduced compared with normal clinical care in people with Type 1 diabetes.[289] However, age differences between the control and intervention groups at baseline mean that this study is possibly methodologically limited.

Another moderate sized systematic review of eight trials encompassing over 3,000 patients with either Type 1 or Type 2 diabetes, found that intensive versus brief education on foot care provided a significant decrease in incidence of foot ulcers, and in one trial amputations, but no difference in the same outcomes over seven years in another study.[506] This is despite three trials reporting successful uptake of messages regarding foot care behaviour. Another trial reported in this review found that an intensive educational intervention including both people with diabetes and doctors improved the prevalence of serious foot lesions compared to usual care, although the composite outcome of all foot lesions and amputations was not significantly improved. Authors of the review noted methodological limitations of the included studies, and outcome reporting times varied between individual trials (**Ia**).

Diabetes self-management education

Evaluation, in a large systematic review, of a range of diabetes self-management education programmes (DSME) compared to normal routine levels in populations of people with diabetes found that interventions based in community gathering places were able to reduce blood glycated haemoglobin (GHb) and fasting blood glucose levels.[374] There is some evidence that they can also improve diabetes knowledge and improve physical activity (minutes of walking). Other trials reviewed that were based in the home setting - half of which included children or adolescents - showed a significant decrease in GHb after DSME, and a borderline beneficial effect on weight for people undergoing DSME as compared to conventional care. Specific analysis in patients with Type 1 diabetes found no significant change in diabetes knowledge with such programmes (**Ia**).

Other educational interventions

A small randomised controlled trial in people with Type 1 diabetes found that an intervention whereby patients received regular telephone contact with a diabetes nurse to alter insulin regimen decreased HbA_{1c} over six months compared to usual care.[493] This difference was not found to be affected by age, sex, or type of diabetes (**Ib**).

Behavioural and education interventions

There are no systematic reviews and few prospective randomised studies that report on methods to improve concordance in self-management in people with Type 1 diabetes. One small unblinded study, which was methodologically limited owing to high drop-out rates and inequalities in patient characteristics at baseline, found that an intervention of a self-taught study programme to improve self-control behaviour was able to demonstrate improved adherence to goals of self-monitoring of blood glucose level over 12 weeks.[240] The intervention included a wide range of educational and behavioural choice items, and the relative effectiveness of any of these is hard to define. The methodological limitations of the study would not form a rigorous basis for recommending such an approach (**Ib**).

A similar intervention among adolescents (mean age 18 years) in India enrolled in a prospective randomised trial with an intervention of 15 hours of individualised learning over three months comprising both behavioural and cognitive strategies based on an operant learning model, found improved adherence on a composite three-item scale, compared to usual care.[309] This improved adherence was mirrored in significantly improved blood glucose level compared to people in the control group. However this study had a small sample size and was unblinded, and it was not possible to determine whether benefits persist after the cessation of the intervention (**Ib**).

Education interventions

One small-to medium-sized randomised trial of a specialist education programme delivered to people with Type 1 diabetes by a team of physicians, dietitians, and specialist nurses found there to be no statistically significant differences in diabetes knowledge or adherence to dietary advice compared to a control group who received conventional diabetes education. Both groups improved in both measures immediately after the completion of the education intervention but then knowledge and adherence fell away with time. This trial was sited in Finland and there may be differences in content of conventional diabetes education compared to that of the UK care setting (**Ib**).[266]

Monitoring devices

There were no significant differences in adherence to glucose self-monitoring or in blood glucose levels reported at six months between two interventions with novel glucose monitoring devices and control with a standard device from a medium-sized multicentre randomised trial.[193] The trial included a population of people with Type 1 diabetes who had had the condition for an average of 14 years. The study was blinded between the two novel monitoring machines, but the people in the control group would have been aware that they were not receiving the intervention as they continued to use their usual machine. To evaluate adherence all patients were asked to keep diaries of self-monitoring behaviour and this may have stimulated greater adherence even in the control group than under normal everyday self-monitoring conditions (**Ib**).

5.1.2 Health economic evidence

Assessing the cost-effectiveness of patient education is complicated by the fact that patient education is rarely assessed in isolation. Recent NICE guidance 353 into patient education models considered the health economic evidence for interventions in terms of self-care, quality of life, and the long-term complications of diabetes. Interventions improving knowledge of diabetes were excluded from consideration, as improved knowledge of diabetes does not necessarily affect subsequent outcomes.

The NICE appraisal found only two published health economic papers suitable for assessing patient education.[170,242] Of these, only one included Type 1 diabetes patients, and this established cost-effectiveness ratios for altering food habits.[170]

5.1.3 Consideration

The group noted that patient education was a necessary and logical part of most aspects of diabetes self-care, and that self-care was a social, health, and economic necessity in the management of the condition. Specific recommendations related to aspects of care such as self-monitoring, insulin therapy, foot care and nutrition were thought best presented in the individual sections of this guideline. The group noted inappropriateness of the classical clinical trial model when just one feature of an integrated package was varied, and one of many possible outputs monitored as primary outcome. There is also the difficulty of, and lack of funding for, the larger, longer-term trials used for pharmaceutical interventions. Equally, the central role of education in achieving success in blood glucose control and health outcomes (DCCT and other key studies) could not be ignored. Such information suggested that educational interventions were likely to be cost-effective, but it was impossible to make comparative judgements of different education models, a conclusion seemingly also reached by the NICE Appraisal Committee on the basis of a report from the University of Southampton's health technology assessment unit.

Issues of information overload at the stressful time of diagnosis, the size of the longer-term educational needs of individuals, the diversity of individual needs, and the retention of the information needed to make informed choices, and the group's experience of these in practice, served to guide recommendations broadly in line with those of Diabetes UK and the International Diabetes Federation (Europe).

Table 109: Appropriate content of education programmes

Some appropriate content of education programmes for people with Type 1 diabetes and those personally involved with helping in their day-to-day care*
Around the time of diagnosis
• The aims of management and outcome of good self-management
• Self-injection and self-monitoring skills
• Nutritional information for people on insulin injection therapy
• Detection and management of hypoglycaemia
• Establishing healthy lifestyle
In the period following diagnosis
• Reinforcement of above
• Use of professional advisors and the healthcare system
• Integration of flexible eating and insulin dosing
• Goals of self-management
• Long-term risks and their amelioration (including arterial risk)
• Management of intercurrent illness and developing complications
• Role of preventative therapeutic interventions, side effects and importance
• Lifestyle issues including employment, travel (including across time zones), driving
• Contraception, pregnancy and children
In the longer term
• Self-care of late complications including foot care

Some appropriate content of education programmes for people with Type 1 diabetes and those personally involved with helping in their day-to-day care*
• Reinforcement based on annual review of need

(a) See also the recommendations of IDF (Europe)[229] and Diabetes UK.[124]

5.1.4 Recommendations

Specific recommendations on patient education and information-giving in particular aspects of care are given in individual sections of this guideline.

7. **A programme of structured diabetes education covering all major aspects of diabetes self-care and the reasons for it should be made available to all adults with Type 1 diabetes in the months after diagnosis, and periodically thereafter according to agreed need following yearly assessment. (Grade A)**

8. **Education programmes for adults with Type 1 diabetes should be flexible so that they can be adapted to specific educational, social and cultural needs. These needs should be integrated with individual health needs as dictated by the impact of diabetes and other relevant health conditions on the individual. (Grade D)**

9. **Education programmes for adults with Type 1 diabetes should be designed and delivered by members of the multidisciplinary diabetes team in accordance with the principles of adult education. (Grade D)**

10. **Education programmes for adults with Type 1 diabetes should include modules designed to empower adults to participate in their own healthcare through:**
    - **enabling them to make judgements and choices about how they effect that care**
    - **obtaining appropriate input from the professionals available to advise them. (Grade D)**

11. **Professionals engaged in the delivery of diabetes care should consider incorporating educational interchange at all opportunities when in contact with a person with Type 1 diabetes. The professional should have the skills and training to make best use of such time. (Grade D)**

12. **More formal review of self-care and needs should be made annually in all adults with Type 1 diabetes, and the agenda addressed each year should vary according to the priorities agreed between the healthcare professional and the person with Type 1 diabetes. (Grade D)**

5.2 Self-monitoring of blood glucose

5.2.1 Rationale

Insulin therapy has to be adjusted with lifestyle, insulin dose requirements vary from individual to individual, and the effects of insulin injections are notoriously erratic. It might seem obvious that

being able to keep an hour-to-hour or day-to-day check on actual blood glucose levels would be to the advantage of any person using insulin therapy. Potential should exist here to assist with diabetes self-education, dose optimisation, reassurance over hypoglycaemia, and helping professionals give optimum advice on insulin regimens.

5.2.2 Evidence statements

Reliability and validity

Papers contained within a systematic review suggest that the evidence on issues of observer training, interdevice variability, the effects of long-term use and patient acceptability have not been adequately addressed (**IV**).[98]

One study within the systematic review comparing self-reported readings against a memory meter showed that inaccuracies in readings were common.[98] This was due to rounding of values, omission of outlying values and reporting of results when no test had been performed. These findings were confirmed in another reviewed study of 14 people who recorded lower blood glucose values in logbook records than meter memories (**Ia**).

Reported within the systematic review, one trial suggested that patients needed to be informed of the memory capacity of their meters to improve accuracy.[98] A further study reported in the review argued that the true diurnal variability in glycaemia in people with Type 1 diabetes is too great to be measured, even when self-monitoring of blood glucose (SMBG) is repeated seven times daily (**Ia**).

Patient factors (as described below) were shown to have an impact (both positive and negative) on the reliability of monitoring in five studies.[98]

Reliability can be improved through proper training of patients, and was shown in sub-group analysis to be equally as good in older people, and people with visual impairments (on condition that extensive instruction has been provided).

One study concluded that as impairment of colour vision affects the ability to interpret self-monitoring with visually read strips, suggesting that all patients should be screened for colour vision before self-monitoring begins (**Ia**).

Clinical effectiveness of blood glucose monitoring

Four trials contained within a systematic review failed to show with sufficient power a demonstrated effect of SMBG on blood glucose control (**Ia**).[98]

Two trials comparing urine and blood testing showed no clinical difference in the two tests (**Ia**).[98]

A systematic review reported on patient preferences for different monitoring techniques.[98] One trial reported patients preferring blood testing, or a combination of blood and urine testing, compared to urine testing alone. No preference was stated for visual strips or strips with meters (**Ia**).

One methodologically limited comparative study comparing blood glucose meters with visual test strips showed patients found the two techniques equally convenient to use, although overall more patients preferred the blood glucose meter.[162]

Preferences were based on: accuracy, confidence in test result, no judgement by patient, inability to cheat with result and use of the built in timer (**Ib**).

One methodologically limited comparative study showed that fructosamine self-test results correlated well with laboratory test with very low bias.[135] Imprecision of the self-test was higher than the laboratory test, but could still identify patients with good versus poor glycaemic control (**DS**).

A further methodologically limited diagnostic study in people with Type 2 diabetes showed self-testing of fructosamine to be comparable in accuracy to laboratory fructosamine and GHb values (**DS**).[78]

One trial with 25 patients showed no significant difference in glucose control or patient practice based on frequency of testing.[178] The authors stated that they are unable to identify any optimal frequency for blood glucose self-monitoring in typical diabetic population. There is little or no relationship between the frequency of blood glucose monitoring, the frequency of insulin dose adjustments and the level of metabolic control (**Ib**).

A study of the preferences of 18 patients within a systematic review reported a preference for testing four times daily, twice weekly or four times daily once a week, compared to twice daily every day of the week (**Ib**).[98]

One study from a systematic review reported fasting plasma glucose to be less useful as an accurate mode of monitoring in insulin treated people with diabetes than in other people (**IIa**).[98]

5.2.3 Health economic evidence

The DCCT included self-monitoring of blood glucose as part of intensive treatment. Self-monitoring is only likely to have an effect on blood glucose control when used to inform the management of diabetes. As such, it is not feasible to analyse its cost-effectiveness in isolation from the requirements of subsequent management strategies.

A recent HTA report[98] identifies one paper considering the cost-effectiveness of blood or urine glucose monitoring against "conventional dietary control" amongst those with Type 1 diabetes.[474] This paper is based on Russian conditions and also includes education in the intervention technologies. The GDG felt that differences in international healthcare systems mean little weight could be placed on its assertions that no significant difference exists between blood and urine glucose monitoring.

5.2.4 Consideration

Self-monitoring does not, in itself, appear to improve blood glucose control. However, the group noted that it was an essential component of the markedly improved blood glucose control with improved outcomes demonstrated in the landmark DCCT study, and indeed in the other smaller studies of blood glucose control and complications. Indeed it was difficult for members of the group to conceive how modern flexible insulin dosage regimens could be adopted without it. However the technique is not easy, painless or convenient, and as a result no one system is found appropriate for use by all individuals. Improved technical facility could be identified from clinical experience. Nevertheless appropriate training and quality of skills review is agreed as necessary and normal practice. Different individuals are noted to use this technology with different frequencies and for different needs according personal preferences. Given the nature of the technology it is rarely abused.

A newer approach, using smaller blood samples from non-finger-prick sites, was not judged to have adequate evidence of reliability, particularly in the situation of hypoglycaemia, to allow a general recommendation.

5.2.5 Recommendations

13. Self-monitoring of blood glucose levels should be used as part of an integrated package that includes appropriate insulin regimens and education to help choice and achievement of optimal diabetes outcomes (D).

14. Self-monitoring skills should be taught close to the time of diagnosis and initiation of insulin therapy (D).

15. Self-monitoring results should be interpreted in the light of clinically significant life events (D).

16. Self-monitoring should be performed using meters and strips chosen by adults with Type 1 diabetes to suit their needs, and usually with low blood requirements, fast analysis times, and integral memories (D).

17. Structured assessment of self-monitoring skills, the quality and use made of the results obtained, and the equipment used should be made annually. Self-monitoring skills should be reviewed as part of annual review or, more frequently, according to need, and reinforced where appropriate (D).

18. Adults with Type 1 diabetes should be advised that the optimal frequency of self-monitoring will depend on:

- **the characteristics of an their blood glucose control**
- **the insulin treatment regimen**
- **personal preference in using the results to achieve the desired lifestyle (D).**

19. Adults with Type 1 diabetes should be advised that the optimal targets for short-term glycaemic control are:

- **a pre-prandial blood glucose level of 4.0–7.0 mmol/l and**
- **a post-prandial blood glucose level of less than 9.0 mmol/l (D).**

Note: These values are different to those given in the recommendations for children and young people with Type 1 diabetes because of clinical differences between these two age groups.

20. Monitoring using sites other than the finger tips (often the forearm, using meters that require small volumes of blood and devices to obtain those small volumes) cannot be recommended as a routine alternative to conventional self-blood glucose monitoring (D).

5.3 Dietary management

5.3.1 Rationale

The imperfect nature of insulin replacement therapy, and in particular the prospective, erratic and inappropriate profiles of insulin absorption, make it necessary to understand the effects of different foods on glucose excursions if these excursions are to be appropriately minimised. Furthermore, people with Type 1 diabetes are at high arterial risk, which might be ameliorated by appropriate nutritional choices, while some associated conditions can be partly managed through nutritional advice.

5.3.2 Evidence statements

Changes to diet

Four small randomised controlled trials were identified examining different diet regimens in people with type 1 diabetes.[82,165,195,320] One randomised controlled study found that a high fibre diet (50g/day) for 24 weeks compared to a low fibre diet (15 g/day) improved blood glucose profile, and number of hypoglycaemic events, although HbA1c, cholesterol, body weight, and insulin dose were not affected (**Ib**).[165]

A high carbohydrate, high fibre and low fat diet, compared to conventional low carbohydrate diet, taught by a dietitian in an unblinded randomised controlled trial was seen at 12 months to improve HbA1c (**Ib**).[320]

The addition of vitamin E to the normal diet has been shown to provide no benefit in terms of cholesterol level, HbA1c, body mass index (BMI), insulin dose, or blood pressure over a 12 month period (**Ib**).[82]

There were significant improvements in glomerular filtration rate, and a decline in albuminuria after 4 weeks of a low protein diet compared to a normal protein diet in a randomised prospective trial in people with overt diabetic nephropathy.[195] Outcomes of urinary sodium excretion, blood pressure, BMI, and HbA1c were not significantly different between the diets (**Ib**).

Therapy adjustment for normal eating

Canadian clinical practice guidelines recommend that all people with diabetes on fixed-dose insulin regimen should have an individualised meal and activity plan developed.[531] Two studies showed that patients should be taught how to adjust insulin dosage, diet and physical activity in response to blood glucose levels, to reduce incidence of hypoglycaemia (**Ia**).

A medium-sized randomised controlled trial of a five-day outpatient programme to enable patients to replace insulin by matching it to desired carbohydrate intake amongst adults with type 1 diabetes found that the intervention improved HbA1c compared to a control of normal care to six months.[33] Positive effects were also seen in weighted quality of life and total well-being. There was no effect on incidence of severe hypoglycaemia, weight or total cholesterol. This trial enrolled people with poorly controlled diabetes (**Ib**).

A similar small trial in which intensified insulin plus simplified diet was compared to conventional therapy and diet found HbA1c to be significantly reduced, although there was no difference between the study groups for outcomes of body weight, BMI, cholesterol, or triglycerides (**Ib**).[82]

Undefined diet

A large cohort study comparing degree of liberalisation of diet away from a specific controlled diet after a treatment and teaching programme with estimation of carbohydrate intake and subsequent insulin self-adjustment found that there was no significant relationship between BMI and degree of diet liberalisation.[347] In addition there was no relationship with HbA1c level or severe hypoglycaemia. However there was a relationship between liberalised diet and higher cholesterol levels, and an inverse relationship with tendency to monitor blood glucose more than three times a day (**IIa**).

Other evidence

The recent evidence-based guidelines for nutrition principles developed by the ADA, provide a broad overview of research in the area of improved diabetes care for people with Type 1 diabetes through beneficial nutritional therapies.[32] There are recommendations based on well-performed RCTs showing significant effectiveness of interventions for areas such as carbohydrates, dietary fat, energy balance and obesity, nutritional therapy for the treatment or prevention of acute complications, and hypertension. Recommendations in other key areas are based on cohort or uncontrolled studies (**Ia**).

5.3.3 Health economic evidence

The recent NICE Technology Appraisal into patient education models (http://www.nice.org.uk/cat.asp?c=68326) recommends dose adjustment for normal eating (DAFNE), and the intensified treatment required by DAFNE, as cost-effective.[361]}

5.3.4 Consideration

The group was impressed by the systematic approach to nutritional recommendations published by the ADA,[32] and the consistency of that approach with the new recommendations from Diabetes UK.[95] Consideration of the existing guidelines in the area did not lead the Group to any divergent recommendations on nutrition. Furthermore recent NICE guidance on education models for people with Type 1 diabetes had particularly addressed the relevance of one programme for meal-time insulin dose adjustment (DAFNE), and, after due discussion of some of the issues surrounding that study, including the health economic issues, it was felt inappropriate to recommend modification of any of the appraisal's conclusions. Accordingly the recommendations agreed by the Group are mainly those of emphasis and approach appropriate to people with Type 1 diabetes, but reflecting both management of blood glucose excursions and arterial risk.

5.3.5 Recommendations

21.Programmes should be available to adults with Type 1 diabetes to enable them to make:

- **optimal choices about the variety of foods they wish to consume**
- **insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods (A).**

22.Information should also be made available on:

- **effects of different alcohol-containing drinks on blood glucose excursions and calorie intake**
- **use of high calorie and high sugar 'treats'**
- **use of foods of high glycaemic index (D).**

23. Information about the benefits of healthy eating in reducing arterial risk should be made available as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. This should include information about low glycaemic index foods, fruit and vegetables, and types and amounts of fat, and ways of making the appropriate nutritional changes (D).

24. All healthcare professionals providing advice on the management of Type 1 diabetes should be aware of appropriate nutritional advice on common topics of concern and interest to adults living with Type 1 diabetes, and should be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include:

- **glycaemic index of specific foods**
- **body weight, energy balance and obesity management**
- **cultural and religious diets, feasts and fasts**
- **foods sold as 'diabetic'**
- **sweeteners**
- **dietary fibre intake**
- **protein intake**
- **vitamin and mineral supplements**
- **alcohol**
- **matching carbohydrate, insulin and physical activity**
- **salt intake in hypertension**
- **co-morbidities including nephropathy and renal failure, coeliac disease, cystic fibrosis, or eating disorders.**
- **use of peer support groups (D).**

6 Blood glucose control and insulin therapy

6.1 Clinical monitoring of blood glucose

6.1.1 Rationale

Type 1 diabetes is for the most of the time asymptomatic once effective therapy is instituted. However it is generally understood that there is a relationship between blood glucose control and the late complications of the condition. Together these observations suggest that some means of monitoring blood glucose control should help health-care professionals advise people with diabetes to best effect on insulin doses, regimens, and associated lifestyle issues.

6.1.2 Evidence statements

Glycated haemoglobin testing

A Diabetes UK consensus statement recommended that only HbA1c should be used in the monitoring of blood glucose control. Other studies reported within a systematic review have shown discrepancies in the classification of patients between HbA1c and HbA1 assays (**IV**).[98]

Two studies in a systematic review showed high intra-individual variability for GHb assays in non-diabetic and in diabetic subjects with stable or variable control.[98] One of these studies suggested an association between clinical control and sampling interval (**IIa**).

The same systematic review reported on randomised controlled trial evidence supporting the use of GHb measurements, in particular results cited from the DCCT demonstrated the usefulness of these assays in contributing to improved long-term blood glucose control and a reduction in morbidity (**Ia**).[98]

A Danish systematic review reported that HbA1c values allowed clinicians to identify patients with poor glycaemic control, concluding that GHb is the most clinically appropriate test of long-term glycaemia and should be used in routine management of Type 1 diabetes (**Ia**).[277]

Frequency of monitoring

The optimal frequency of testing has not been established.

One study within a systematic review recommended that no more than six GHb assays were necessary in a given year (**IV**).[98]

ADA recommendations advise GHb measurements are performed in accordance with clinical judgements.[32] ADA consensus recommends GHb testing at least twice a year in patients with stable glycaemic control who are meeting treatment goals. Testing should be more frequent (quarterly) in patients whose therapy has changed or who are not meeting glycaemic control targets (**IV**).

Fructosamine testing

There are discrepancies in the evidence surrounding the use of fructosamine testing.

One study within a systematic review reported fructosamine testing as able to detect shorter or more recent fluctuations in blood glucose compared to GHb.[98] Fructosamine testing does not have the problems of standardisation associated with GHb, thus results are comparable between laboratories (**IIa**).

Two studies within a systematic review described a high correlation between fructosamine and HbA1c, however, later studies debated this claim.[98] One study suggested that although fructosamine correlates with HbA1c, the value of HbA1c in an individual has been shown to not routinely be inferred with reliability from the level of fructosamine (**IIa**).

Two studies contained within a systematic review, in patients with renal failure and elderly Type 2 diabetes patients with liver cirrhosis and nephrotic syndrome, suggest the influence of chronic conditions rather than metabolic control on fructosamine levels is the source of unreliability in test result.[98] The systematic review concludes that more evidence is needed to resolve these issues (**IV**).

One correlation study within a review showed no significant correlation between HbA1c and fructosamine results over a six month follow up (**III**).[98]

Frequency of monitoring

ADA recommendations state that assays of glycated serum protein would have to be performed on a monthly basis to gather the same information as measured in GHb three to four times per year (**IV**).[32]

A systematic review urges caution in using fructosamine testing, in light of the fact that fructosamine values can be improved by increased concordance a week or two before testing (**IV**).[98]

Another study found that fasting blood glucose levels (FBG) and serum fructosamine are not as useful as HbA1c for monitoring diabetic control, but are additional extras for assessing control over short and long periods (**IIa**).[98]

Continuous glucose monitoring systems (CGMS)

Three observational studies compared continuous glucose monitoring systems (CGMS) with SMBG.[184,185,305] Studies demonstrated good correlation of CGMS with plasma and capillary measures of blood glucose over a range of blood glucose values. Error grid analysis showed the majority of readings fell within a clinically acceptable margin of error across all studies (**III**).

One study reported acceptable level of comfort with CGMS. However, none of these studies address viable outcomes of glycaemic control or long-term use.[305] Study methodology is not clearly reported.

Near patient testing

In this guideline, 'near patient testing' is defined as a biochemical or other test at or near (in time and place) the clinical consultation, such that the result is available at the consultation.

One controlled trial within a systematic review demonstrated that near patient testing led to an increase in management changes for patients with poor glucose control.[182] Near patient testing for HbA1c improved the process of care of patients (**IIa**).

In the same review, questionnaires recording patient satisfaction of near patient testing concluded that the introduction of near patient testing for HbA1c improves the likelihood of monitoring and

discussion of glycaemic control at patient visits.[182] Patients reported that this was important to them and resulted in greater satisfaction with the test information provided (**III**).

Within the health technology assessment a retrospective cohort study showed that, after allowing for confounding factors, mean HbA1c level was lower following near patient testing and the immediate availability of results.[182] In order to precisely quantify the effect of the testing system on HbA1c level, further, prospective studies are required (**IIa**).

A systematic review reported four studies on the effectiveness of benchtop analysers compared with traditional laboratory methods.[98] Two studies showed comparable results between the two techniques when operated by non-medical personnel. One study found that the benchtop analyser, although reliable, tended to slightly underestimate HbA1c, compared with high performance liquid chromatography (HPLC) (**IIa**).

6.1.3 Health economics evidence

An HTA report produced cost estimates for near patient testing conducted by a laboratory or nurse against conventional testing.[182] However, little data was available on the effects of near patient testing on clinical or quality of life outcomes. For health economics to provide guidance in this area, the long-term effects of different types of clinical monitoring on glycaemic control and subsequent complications must be known.

A recent HTA report recommended further research into the cost-effectiveness of near patient testing for diabetes, FBG and fructosamine testing.[98] No other paper in the health economics searches specifically addressed the issue of clinical monitoring.

6.1.4 Consideration

The group endorsed the utility of having a frame of reference against which people with diabetes and the professionals advising them could assess risk and risk threshold for micro- and macro-vascular disease in terms of blood glucose control. This was a core component of intensification of therapy in studies showing improved long-term outcomes. HbA1c is the only measure for which quantitative information linking glucose control to complications is available, and then only when standardized to the assay used in the DCCT study. Near patient testing was felt to be a core component of making optimal and relevant use of HbA1c results. Continuous glucose monitoring systems were considered to not yet have established their usefulness beyond problem-solving in the occasional person with recurrent blood glucose control problems at the same time of day.

6.1.4.1 Recommendations

R38: Clinical monitoring of blood glucose levels by high precision DCCT-aligned methods of haemoglobin A1c (HbA1c) should be performed every two to six months depending on:

- achieved level of blood glucose control
- stability of blood glucose control
- change in insulin dose or regimen (**D**).

R39: Site-of-care measurement, or before clinical consultation measurement, should be provided (**D**).

R40: HbA1c results should be communicated to the person with Type 1 diabetes after each measurement. The term "A1c" can be used for simplicity (**D**).

R42: Fructosamine should not be used as a routine substitute for HbA1c estimation (**B**).

R43: Continuous glucose monitoring systems have a role in the assessment of glucose profiles in adults with consistent glucose control problems on insulin therapy, notably:

- repeated hyper- or hypo-glycaemia at the same time of day
- hypoglycaemia unawareness, unresponsive to conventional insulin dose adjustment (**B**).

6.2 Glucose control assessment levels

6.2.1 Rationale

The DCCT, and a number of smaller studies which are potentially underpowered, suggest that more intensive management of people with Type 1 diabetes (by themselves, with advice) reduces the rate of development of microvascular complications over a period of years.[513] The primary metabolic improvement in the DCCT was lowering of blood glucose level, and this was the measure used in that study to drive the intensification of therapy. This suggests that using measures of blood glucose control in the routine management of therapy in people with Type 1 diabetes is well founded.

A question then arises as to what level of blood glucose control people with diabetes should choose to strive for. A closely related question is what level(s) of glucose control should be used in assessing the performance of diabetes services.

'Targets' have been criticised by some as not giving flexibility for individuals with particular problems (e.g. hypoglycaemia) to be content with higher HbA1c levels, which allow some longer-term risk for a gain in current well-being. It is clearly useful to be able to identify those in whom newer and more expensive technologies could be tried in an attempt to reduce microvascular risk, and to distinguish them from those who already achieve safe (or safer) levels on their current therapy. People with diabetes need information on what blood glucose level they need to attain if they wish to minimise vascular risk.

6.2.2 Evidence statements - guidelines

In 1989, the European NIDDM Policy Group (Type 2 diabetes) suggested HbA1 was good <8.5 %, acceptable 8.5-9.5 %, poor >9.5 % (equivalent to HbA1c of <6.9, 6.9-7.7, >7.7 %). No evidence for these limits was given, and it was not clear whether the intent was for micro- or macro-vascular protection or both. However, the need to individualise by life expectancy was acknowledged (**IV**).[27]

In 1993, the above guidelines were revised to HbA1c <6.5 %, 6.5-7.5 %, and >7.5 %. The European IDDM Policy Group (Type 1 diabetes) (WHO, IDF, St Vincent) met concurrently and agreed these, but using the terminology 'good', 'borderline' and 'poor' to describe the groups. These pre-DCCT recommendations are not justified in the text.[8] See Table 110, below, for how that guideline maps these assessment levels to self-monitored blood glucose equivalents.

Table 110: Blood glucose equivalents (self-monitored) of HbA1c assessment levels, as given in the 1993 European IDDM Policy Group guideline

HbA1c (%)	Pre-prandial (mmol/l)	Post-prandial (mmol/l)
6.5	6.1	8.0
7.5	8.0	10.0

In 1998 the European Diabetes Policy Group revised its terminology to 'assessment levels', giving advice on how to use assessment levels to set targets for individuals. These were, for (HbA1c): adequate 6.2-7.5 %, inadequate >7.5 %. However the relation of this 7.5 % to glucose levels was then revised to equivalent to a self-monitored pre-prandial level of 6.5 mmol/l and post-prandial 9.0 mmol/l. These post-DCCT recommendations are not justified in the text (**III**).[8]

The NICE (inherited) Type 2 diabetes guideline on glucose control reads:

Evidence: narrative

The UKPDS showed that the reduction over a median of 10 years in HbA1c from 7.9 to 7.0 % using sulphonylureas or insulin provided much of the benefit that could be expected from that degree of improved glycaemic control. However it also illustrated the difficulties in being able to reach this level (7.0 %) in a substantial proportion of people. Thus providing only one target is likely to encounter a significant number of people who 'fail' to meet that target. Similarly for some individuals an even lower target is desirable as they may have additional risk factors that necessitates even tighter blood glucose control. The UKPDS also suggested that there were no thresholds for cessation of benefit and that the lower the level of mean HbA1c the better.

Working group commentary

The Working group tried to reflect these issues when deciding upon a target HbA1c. They concluded that a range was the best option, recognising the difficulty in achieving a low target whilst recognising the importance of trying to achieve as near normal an HbA1c level as possible, and in particular recognising that additional risk factors made the lower limit even more important for many individuals. While no study suggests clear thresholds, the group noted on the basis of the epidemiological evidence in the DCCT (Type 1 diabetes) and UKPDS that microvascular risk was low once average HbA1c was around 7.0-8.0 % while arterial risk continued to fall down to 6.0 to 7.0 % (DCCT standardised).

Thus the target for each individual should be set which fully takes into account: their assessed risk factors, including: age, BMI, blood pressure and lipid status; side effects of therapy, other individual factors, patient choice (**NICE**).[323]

The NICE Type 2 diabetes guidelines therefore recommended 6.5 to 7.5 % as ideal targets, individualized by balance of macrovascular (tend to 6.5 %) and microvascular (7.5 %) risk (**NICE**).

The ADA has republished its recommendations yearly.[32] These choose a 'glycaemic goal' of HbA1c <7.0 % for adults (type of diabetes not specified), equating this to pre-prandial <7.2 mmol/l and peak post-prandial <10.0 mmol/l. However, a table in the same paper suggests that an HbA1c of 7.0 % equates to mean self-monitored plasma glucose of 9.5 mmol/l116 (**IV**).

However in the same issue (January 2003) the ADA notes in a chapter on 'Implications of the DCCT' that the level of glucose control to be sought under ideal circumstances is an HbA1c of around 7.2% (average glucose 8.6 mmol/l).[32] This argument is, however, based on that achieved in the DCCT, and is thus not theoretically justified (**IV**).

The microvascular risk threshold is what determines the diagnostic threshold for diabetes. In theory, oral glucose tolerance test (OGTT) findings should give some guidance as to this threshold. Unfortunately these are mainly based on non-physiological glucose load findings, and set a top limit of risk for 2h post-prandial levels. Fasting levels have been set as a microvascular threshold of 7.0 mmol/l (based on epidemiological equivalence with 2h OGTT levels), which would map to a DCCT-harmonized HbA1c of about 7.7 % (**IV**).

6.2.3 Evidence statements

Simple direct findings indicating the microvascular risk level for people with Type 1 diabetes are not available.

The DCCT data has never been satisfactorily analysed with a view to answering this question. A graph in the original main paper suggests a curvilinear relationship between control and complications, giving the conclusion that lower is always better (ignoring the hypoglycaemia issue for this purpose), down at least to the levels measured in the study (5.5 %).[490] This conclusion is called into question because:

- it is based on study averages, and even people at lower levels over nine years may have been at high levels at times
- it takes no account of pre-trial levels
- incident retinopathy is counted only in a forward (worsening) direction, which makes no allowance for false negative retinopathy at baseline
- worsening retinopathy is known to occur in the first 2 years after improvement of blood glucose control, and this is not discounted (**IIa**).

Further analysis was published in 1995.[4] Unfortunately this is mostly in the form of a series of fitted curves without the data on which they are based. Curves of risk versus time suggest that retinopathy progression in the intensively managed group did not increase with time with a mean HbA1c of 8.0 %, and increased little at this level in the conventionally managed group with time (**IIa**).

Reanalysis of the published DCCT curve118 suggests no worsening of retinopathy rates from normal levels until HbA1c >8.0 %; the 'low' rates (2 % per 100 patient years) below that may be artefact for the reasons given above. The UKPDS (epidemiological analysis, Type 2 diabetes, microvascular disease) suffers much the same problems.[480] A similar level is found for retinopathy of 2 % per 100 patient years at an HbA1c of 7.5 % and of 1 % per 100 patient-years at a level of 6.5 % (**III**).

One study (1989) studied HbA1 and retinopathy incidence long-term in Belfast.[316] While some clear relationships were established the data showing no proliferative retinopathy below an HbA1 of 10.0 % (HbA1c 8.5 %) are compromised by very small numbers, and only interquartile ranges are given for non-proliferative retinopathy (**III**).

Neither the Oslo nor Stockholm studies of control and complications in Type 1 diabetes give useful data on targets and thresholds, beyond showing that people with lower levels on average do better (**III**).[424]

A non-randomised controlled study looked prospectively at glycated Hb and microalbuminuria risk in people with Type 1 diabetes attending their clinic.[267] Their data did suggest a threshold effect (small and unchanging incidence below threshold, sharp rise above), at 7.9-8.5 % HbA1c (the authors chose to centre on 8.1 %) (**IIa**).

A non-randomised controlled study looked at how glycated Hb measurement related to OGTT results, performing a meta-analysis on 18 studies.[399] Unfortunately most of these were published before any kind of GHb standardisation, rendering the results uninterpretable (**IIa**).

A further cohort study looked in more detail at GHb, fasting and 2h glucose as diagnostic methods (and thus mainly Type 2 diabetes), using retinopathy and nephropathy as outcome measures.[317] It may be noted that the Wisconsin data suggested that the microvascular/glucose control relationships were the same in Type 1 and Type 2 diabetes. The data presentations are strongly reminiscent of previous work, with low and unchanging incidence of microvascular disease up to an inflection point, then sharply rising rates.[267] The thresholds for fasting glucose appear to be somewhere above 6.8 mmol/l (consistent with older OGTT data), and HbA1c somewhere above 7.4 % (and below 9.1 %) (**IIa**).

Glucose equivalents

Two non-randomised controlled studies report the relationship between HbA1c and self-monitored pre- and post-prandial glucose levels.[352,435] The reports are consistent and can be related to DCCT-harmonised assays. It must be noted that these studies used pre-determined self-monitored profiles taken from memory meters, and cannot easily be translated into patient-selected estimations, or only pre-prandial monitoring. They also omit the effects of night-time glucose profiles between bedtime and pre-breakfast readings. These data give the most robust evidence of the relationship between HbA1c and the toxic glucose concentrations which actually cause the microvascular damage (**IIa**).

6.2.3.1 Consideration

There must be a threshold for glucose control and the development of microvascular complications, or non-diabetic people would get complications. Indeed this threshold must be well above the normal range as people with impaired glucose tolerance (IGT) do not (by definition) get microvascular complications. As people with IGT have HbA¬1c levels of up to 7.0 %, this by itself sets a lower limit of microvascular risk.

The microvascular thresholds of HbA1c 7.5 % set around 10 years ago have stood the test of all data published since. If anything the DCCT, Krolewski and McCance data suggest a figure closer to 8.0 %.

Recommendations from the ADA (7.0 %) and American College of Endocrinologists (6.5 %) are not type of diabetes specific; data does suggest macrovascular protection is gained by lowering blood glucose levels into the normal range, and the NICE (inherited) guidelines for Type 2 diabetes go for HbA1c 6.5 % in these higher arterial risk individuals.

Some people with Type 1 diabetes are at higher arterial risk, notably those with developing nephropathy. This can be identified by increased albumin excretion rate. The presence of features of the metabolic syndrome will also predict higher arterial risk. It may be appropriate to consider tighter targets for glucose control (if feasible) in people in these categories.

However these levels are better considered as *assessment levels*, to be used in setting realistic targets for the individual. Major diabetes services in Europe currently only get about 20 % of people with Type 1 diabetes into the sub-7.5 % bracket. UK composite data (UKDIABS) shows some services doing better, but this may only represent non-standardised GHb estimation.

That current technologies of diabetes care markedly limit the proportion of people on insulin who were able to manage themselves to ideal levels was not seen as a bar to setting such assessment levels. It was noted that arterial risk would be likely to have a different relationship in this regard from microvascular risk, and that for the former there was little direct information available for people with Type 1 diabetes, but that the understandings gained in Type 2 diabetes and people without diabetes gave strong guidance in this respect. It was felt that as the assessment of the evidence available pointed to target definition in the same range as other published guidelines, and in particular the NICE inherited guidelines for Type 2 diabetes, there was practical utility for practice of care in having matching recommendations. Lastly the problem of hypoglycaemia in limiting was what achievable in any individual should be addressed within any recommendations, to assuage inappropriate attempts to achieve tight control and counter impressions of failure if targets are not attained.

6.2.4 Recommendations

25. Adults with Type 1 diabetes should be advised that maintaining a DCCT-harmonised HbA1c below 7.5 % is likely to minimise their risk of developing diabetic eye, kidney or nerve damage in the longer term. (B)

26. Adults with Type 1 diabetes who want to achieve an HbA1c down to, or towards, 7.5 % should be given all appropriate support in their efforts to do so. (D)

27. Where there is evidence of increased arterial risk (identified by a raised albumin excretion rate, features of the metabolic syndrome, or other arterial risk factors) people with Type 1 diabetes should be advised that approaching lower HbA1c levels (for example 6.5 % or lower) may be of benefit to them. Support should be given to approaching this target if so wished. (NICE)

28. Where target HbA1c levels are not reached in the individual, adults with Type 1 diabetes should be advised that any improvement is beneficial in the medium and long term, and that greater improvements towards the target level lead to greater absolute gains. (B)

29. Undetected hypoglycaemia and an attendant risk of unexpected disabling hypoglycaemia or of hypoglycaemia unawareness should be suspected in adults with Type 1 diabetes who have:

- **lower HbA1c levels, in particular levels in or approaching the normal reference range (DCCT harmonised <6.1 %)**
- **HbA1c levels lower than expected from self-monitoring results. (D)**

30. Where experience or risk of hypoglycaemia is significant to an individual, or the effort needed to achieve target levels severely curtails other quality of life despite optimal use of current diabetes technologies, tighter blood glucose control should not be pursued without balanced discussion of the advantages and disadvantages. (D)

Note: A new chemical standard for HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This reads lower by around 2.0% (units), and will be the basis of primary calibration of instruments from 2004 onwards. However, this does not preclude the use of DCCT-harmonised levels, and views from patient organisations and professional bodies at a recent Department of Health meeting (July 2003) are that all HbA1c reports should be DCCT aligned, pending some internationally concerted policy change.

6.3 Insulin regimens

6.3.1 Rationale

Type 1 diabetes is an insulin deficiency disease. Physiological insulin delivery is regulated on a minute-to-minute basis, while therapeutic insulin is given a small number of times a day. Furthermore subcutaneous depot insulin preparations have, until recently, not come close to providing the physiological plasma insulin profiles occurring at mealtimes or in the inter-prandial basal state. A number of preparations of mealtime and extended-acting insulins are available, and combining these to suit individual needs, while taking account of preferences for numbers of injections, gives a variety of possible insulin regimens of differing characteristics.

While insulin deficiency is the hallmark of Type 1 diabetes, a few people retain some insulin secretion for a short time (and might therefore benefit from insulin secretagogues). Some glucose-lowering drugs work on gut absorption of nutrients or on the insulin effector tissues, and might therefore be expected to be of benefit in some individuals even when completely insulin deficient and managed on insulin replacement therapy.

6.3.2 Evidence statements

Insulin and insulin analogues

Insulin with the molecular structure of human and animal insulins is currently available. Evidence from the majority of studies reports no significant differences in hypoglycaemic episodes and glycaemic control between the insulin of human and animal chemical structures (**Ia**).[161,244,431]

Conventional two-dose insulin regimens may result in a high frequency of nocturnal hypoglycaemia. Intensified three-dose insulin regimens improves glycaemic control, but often do not improve morning blood glucose (**Ia**).[137]

Continuous subcutaneous insulin infusion (CSII) improves nocturnal and morning glycaemic control compared with multiple daily injection (MDI) regimens. With multiple injection regimens the morning injection must not be delayed. Total and bolus insulin doses required are lower with CSII compared with MDI (**Ib**).[191]

Mortality from acute metabolic causes (ketoacidosis) was reported as significantly increased with intensified treatment; odds ratio 7.20 (pumps) 1.13 (multiple daily injection).[137] The pump data is however based on early pump technologies (**Ia**).

Similar glycaemic control results from either lente or isophane (NPH) insulin when used as basal insulin for multiple injection regimens together with a short-acting insulin preparation before meals (**Ib**).[496]

On the balance of effectiveness and cost-effectiveness evidence, insulin glargine, which has a peakless action profile, is also recommended as a long-acting preparation for people with Type 1 diabetes[360]; some studies in this review show significantly lower fasting blood glucose with insulin glargine than isophane (NPH) insulin and others suggest that people on insulin glargine may experience fewer hypoglycaemic events than people receiving once-daily isophane (NPH) insulin (**NICE**).[360]

Evidence from a large multicentered study suggests that people commonly inject insulin closer to meal-time than the recommended 30 minutes. Due to slow absorption and delayed action, the use of unmodified ('soluble') human insulin as pre-meal dose results in high and variable post-breakfast blood glucose concentrations, which together with the incidence of later hypoglycaemia suggests that this regimen does not give satisfactory post-prandial blood glucose control in many patients (**Ib**).[509]

Rapid acting insulin analogues allow injection closer to meal times due to their pharmacokinetic profile (**Ib**).[121,295,372]

A meta-analysis[115] and several open-label trials[39,134,158,274,402,428,433,434,509] show that Insulin lispro is more effective than unmodified ('soluble') human insulin in improving post-prandial glucose control, without an increase in the rate of hypoglycaemic episodes(**Ia**).

Two studies[25,217] show reduced frequency of nocturnal hypoglycaemia[70] with insulin lispro compared to unmodified ('soluble') human insulin (**Ib**).

Two studies show reduced frequency of severe hypoglycaemia with insulin lispro compared to unmodified ('soluble') human insulin (**Ia**).[70,460]

Patients perceive an improvement in their well-being and quality of life with rapid-acting insulin analogues due to flexibility of injection times and less frequent hypoglycaemic reactions (**Ib**).[217,244,428]

The effects of insulin lispro on HbA1c levels (overall glycaemic control) have not been firmly established.291, 1064 275 [115,460,509] The long-term safety profile is as yet unknown (**Ia**).

Two multicentre randomised studies[220,460] and one RCT[295] showed insulin aspart to improve post-prandial glucose control more effectively than unmodified ('soluble') human insulin, without an increase in the rate of hypoglycaemic episodes. Fewer major hypoglycaemic episodes were observed (**Ia**).

A before-and-after study has shown that a lower dose of meal time insulin can be taken along with an increase in basal dose, with no increase in hypoglycaemic episodes when insulin lispro is used as a replacement for human insulin as meal-time injection therapy (**IIb**).[134]

Two randomised trials have shown that it is possible to replace mealtime unmodified ('soluble') human insulin with insulin lispro or insulin aspart without detriment to glycaemic control if care is taken to replace basal insulin delivery more physiologically (**Ib**).[207,539]

A multi-arm randomised trial found that adding a few units of isophane (NPH) insulin to insulin lispro at each meal, in combination with bed-time isophane (NPH) insulin improves blood glucose concentrations compared to an unmodified ("soluble") human insulin regimen in the a multidose regimen (**Ib**).[121]

Splitting the evening administration of insulin to short-acting insulin at dinner and isophane (NPH) insulin at bedtime has a number of advantages over mixed administration of short-acting insulin and isophane (NPH) at dinner. Compared with the mixed mealtime regimen, the evening split regimen reduced by more than 60% the risk of nocturnal hypoglycaemia; improved long-term control of blood glucose levels; decreased variability of blood glucose levels in fasting state and led to improvement in preserved hormonal, symptom and cognitive function responses to hypoglycaemia (**Ib**).[143,472]

When basal insulin replacement is by either continuous subcutaneous insulin infusion (CSII) or multiple daily administrations of isophane (NPH) insulin, the long term administration of lispro at mealtime reduces HbA1c; however, compared with multiple daily injections, patients using continuous subcutaneous administration of insulin (mainly those using older systems) have been at a significantly higher risk of ketoacidosis (**Ib**).[191]

Frequency of hypoglycaemic reactions were found to be similar on patient-mixed and premixed insulins.[133,433] One randomised controlled trial showed premixed preparations of insulin analogues to be well suited for those who wish to limit the number of daily injections; 83% of people expressed a preference for premixed insulins throughout the trial (**Ib**).[133]

Few studies have addressed the needs of people with diabetes with suboptimal glucose control, and none of suitable design from the evidence hierarchy were found for review.

In a group of people with Type 1 diabetes with poor glucose control, the introduction of more intensive insulin regimens may lead to high loss to follow-up.[123]

Poor outcome appears to be due to the people refusing the constraints of multiple daily injections, effective blood glucose self-monitoring, and regular clinic visits at short time intervals. It was suggested that people should be given clear and concise information on treatment goals and the ways in which these goals are to be attained as well as an explanation of the advantages and disadvantages (**IV**).

Few studies addressed the needs of people newly diagnosed with diabetes and none of suitable design from the evidence hierarchy were found for review.

Acarbose and insulin combination therapy

Four randomised controlled trials, two large parallel group,[216,430] and two small crossover designs[307,510] were identified that examined the use of acarbose in conjunction with insulin therapy compared to insulin and placebo in each case, in people with Type 1 diabetes. A multicentred study with variable doses titrated up to 300 mg three times a day for 24 weeks, found a significant reduction in HbA1c levels with acarbose compared to placebo, and decreases in fasting and post-prandial glucose levels to two hours.[216] There were no differences between groups for daily insulin dose or hypoglycaemic events, although adverse events of abdominal pain, diarrhoea, and flatulence were more common with acarbose. This led to more frequent treatment discontinuation in the acarbose group than the placebo group. A similar Italian trial with up to 100 mg acarbose three times daily for 24 weeks found no difference in HbA1c levels, daily insulin dose, fasting glycaemia, and total cholesterol.[430] However, a significant decrease was found in two-hour post-prandial plasma glucose level, and HDL cholesterol levels were lower in people on acarbose than placebo. Again minor adverse events were more common in the acarbose group, but hypoglycaemic episodes were similar in both groups. Although care was taken not to alter baseline insulin doses, this could be adjusted if glucose levels exceeded 11.1 mmol/l or reduced with hypoglycaemic episodes (**Ib**).

The two cross-over trials with 100 mg acarbose three times a day over relatively short time period did not assess requirement for wash out periods (although analysis in one found no effect of treatment order) and did not account for study withdrawals. One study found a benefit in terms of HbA1c with acarbose,[307] while the other found no significant differences between groups.[510] Potential methodological limitations of these trials would not permit them to be used as an evidence base to inform recommendations in this area (**Ib**).

Sulfonylurea and insulin combination therapy

Two small randomised controlled trials investigated the use of glibenclamide (called ‘glyburide’ as the trials were conducted in the USA) in the therapy for Type 1 diabetics. A study using 5 mg glyburide (orally) for 12 weeks compared to placebo after a 12-week open label insulin stabilisation

run-in period found fasting blood glucose declined significantly at 12 weeks from baseline, although no comparison was made between groups.[189] No differences were found in daily insulin dose or glycated haemoglobin levels at any stage of the study. A randomised study without comparison between groups at baseline with 5 mg glyburide daily for 24 weeks compared to placebo found no differences in plasma C-peptide levels between groups, nor difference in plasma glucose concentrations at any time point.[172] Although HbA1c levels were reported to have changed more from baseline in the glyburide treated group at six weeks, potential methodological limitations of these trials would not permit them to be used as an evidence base to inform recommendations in this area (**Ib**).

Comparison of 15 mg of glibenclamide daily with placebo in addition to insulin therapy in a small sample of people with Type 1 diabetes in a randomised double-blind cross-over study found mean blood glucose level, HbA1c, and blood glucose variability to be significantly lower with the intervention among people who retained endogenous insulin production.[71] No such differences were found in a subgroup who were C-peptide negative. Although the study had a medium term intervention period of three months, it did not provide analysis of the cohort as a whole for glibenclamide *vs* placebo and thus cannot be used for recommendations given the small sample sizes of the subgroups, and the inherent difficulties of extrapolating such findings to a wider population (**Ib**).

A reduced insulin requirement at 18 months was found in patients given 80 mg gliclazide twice a day compared to placebo in a small sample in a long-term study.[142] Although glycated haemoglobin both fasting and one hour post-breakfast were found to be very similar in both groups, the gliclazide group had C-peptide levels significantly higher than people on placebo for the same test times of the day, at six-monthly assessment points to 18 months. This study only applies to people with retained endogenous insulin secretion, and thus not the overwhelming majority of people with Type 1 diabetes (**Ib**).

Metformin

A medium-sized randomised controlled study found that the addition of metformin to an insulin regimen provided by CSII was able to reduce the total IR required by the person with Type 1 diabetes (including reduced basal therapy) as compared to placebo over a period of six months. This was achieved without significant change to HBA1c or increased incidence of hypoglycaemia (**Ib**).

6.3.3 Health economic evidence

The health economic searches produced no studies giving guidance on appropriate insulin regimens for those newly-diagnosed with Type 1 diabetes or for the management and prevention of hypoglycaemia, with the exception of the NICE appraisal of insulin glargine.

The health economic searches found no published papers dealing with insulin glargine or NPH insulin. A recent NICE technology appraisal recommended insulin glargine as a long-acting preparation for people with Type 1 diabetes alongside insulin NPH.[360] The crucial issue for the cost-effectiveness of insulin glargine is the amount of utility associated with reducing the fear of hypoglycaemia.

Two cost-benefit studies were identified that considered the role of insulin lispro.[170,491] Neither paper was based in the UK (Canada, Australia), and both suggest that the willingness to pay for insulin lispro will outweigh its additional cost. The cost-effectiveness of lispro is unclear and is likely to be

most favourable amongst those who require increased flexibility in setting meal times, or for whom meal times are often unpredictable.

The issue of the cost-effectiveness of intensive insulin therapy is complicated by a shortage of unconfounded data. The DCCT showed that a series of interventions including intensive insulin therapy reduces the rate of diabetic complications and increases life expectancy amongst an unrepresentative sample of adults and adolescents with Type 1 diabetes. Because of the complexity of this intervention, health economic analysis of the DCCT data has typically assumed that these reductions are primarily due to intensive insulin regimens.

The health economic searches found three models designed to find the cost-effectiveness of intensive treatment,[61,491,530] of which two attempted to form QALYs. The health utility values in each of the studies are poor: in one study 343 non-preference based values are used; in the other[530] only a very small sample was used to find health utilities. Both studies considered only a small number of health states and both suggest that intensive therapy is cost-effective.

Two models analysed intensive treatment in cost-per-life-year terms, and differed in their results. One study[474] produced a cost-per-life-year-figure of US$28,661 at 1994 prices, whilst another[61] found a figure several times larger. Neither study used UK costs. Note that as several diabetic complications will affect quality of life but will not significantly shorten life expectancy, the cost-per-QALY figure may be lower than the corresponding cost-per-life-year figure. Two cost analyses also suggest that the DCCT cost estimates may be overestimates.[187,237] Few inferences that can be drawn from these studies are limited but it appears likely that intensive treatment, including intensive insulin regimens, will be cost-effective.

6.3.4 Consideration

It was noted that Type 1 diabetes is a hormone deficiency disease. The problems faced by people with the condition (injections, hypoglycaemia, hyperglycaemia, consequences of capricious control, late complications) were noted to be solely a function of the poor state of insulin replacement therapy.

The group noted that the use of insulin injections in people with Type 1 diabetes is not RCT-based and never could be. It was also noted that, prior to the introduction of short- and long-acting insulin analogues, the use of insulin regimens based on a combination in various forms of unmodified (soluble) human insulin before meals and human isophane (NPH) insulin for basal supply had become widespread, and that, the analogues aside, there was no evidence to challenge that conventional practice. Long-acting analogues, or rather insulin glargine, are covered by NICE appraisal guidance, and this recommends their availability for use in people with Type 1 diabetes. Rapid-acting insulin analogues are supported by an evidence base for less hypoglycaemia at night and at some other times, reduced hyperglycaemic excursions after meals, and small improvements in HbA1c, suggesting that these too should have an increasing role in people with Type 1 diabetes.

The group was aware that the evidence for combining the advantages of rapid- and long-acting insulin analogues was evolving as the knowledge base to use these technologies improves. This combination would be particularly suitable to matching with active mealtime insulin dose adjustment (AMIDA, see dietary recommendations in 6.3). Some recent NICE technology appraisals provided a health economic basis for supporting this regimen, should appropriate improvements in HbA1c be demonstrated. Accordingly the recommendations were drafted to allow choice of human or combined analogue regimens including from the time of diagnosis.

The group noted the potential usefulness of the new insulins in some special situations, including religious feasts and fasts and shift work. A need to address insulin starters and people who wished for smaller numbers of injections was identified. A need to caution against using more expensive newer insulins in people with control problems without proper assessment of underlying causes was felt appropriate. The NICE appraisal of insulin pumps (effectively an insulin regimen rather than a device) was noted, and no elaboration felt to be needed on that.

The group found the evidence for the general recommendation of any glucose-lowering drug in combination with insulin to be unconvincing. While there may be a small gain in overall glucose control evidenced inconsistently in the acarbose studies, the size of this gain, the prevalence of intolerance, and the suggestion of increased hypoglycaemia, together were taken as indicating that no recommendation for the general use of this drug in this context could be made.

The use of metformin and insulin sensitisers in people with Type 1 diabetes and the metabolic syndrome has not been adequately investigated.

The group was aware of the concern that arterial complications in people with Type 1 diabetes were associated with features of the metabolic syndrome as seen in Type 2 diabetes, and that there was evidence of benefit in people with Type 2 diabetes for some drugs, notably metformin (UKPDS study) and PPAR-γ agonists (see NICE guidance). While not endorsing the general use of such drugs in people with Type 1 diabetes and features of the metabolic syndrome (see section of this guideline on arterial disease management), the group noted that further investigation might support the high *a priori* likelihood of benefit in this high risk situation.

6.3.5 Recommendations

31. Adults with Type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being. (A)

32. Multiple insulin injection regimens, in adults who prefer them, should be used as part of an integrated package of which education, food and skills training should be integral parts. (A)

33. Appropriate self-monitoring and education should be used as part of an integrated package to help achievement of optimal diabetes outcomes. (D)

34. Mealtime insulin injections should be provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues before main meals. (D)

35. Rapid-acting insulin analogues should be used as an alternative to meal-time unmodified insulin: (A)

- **where nocturnal or late inter-prandial hypoglycaemia is a problem**
- **in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.**

36. Basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at mealtimes or the midday insulin dose is small or lacking, the need to give it twice daily (or more often) should be considered. (D)

37. Long-acting insulin analogues (insulin glargine) should be used when and if:

- **nocturnal hypoglycaemia is a problem on isophane (NPH) insulin**
- **morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood glucose control**
- **rapid-acting insulin analogues are used for meal-time blood glucose control. (D)**

38. Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life:

- **biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance**
- **biphasic rapid-acting insulin analogue pre-mixes may give an advantage to those prone to hypoglycaemia at night (D).**

Such twice daily regimens may also help:

- **those who find adherence to their agreed lunchtime insulin injection difficult**
- **adults with learning difficulties who may require assistance from others.**

39. Adults whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations (see R55-R57), and consideration of unusual patterns and combinations (D).

40. For adults undergoing periods of fasting or sleep following eating (such as during religious feasts and fasts or after night-shift work), a rapid-acting insulin analogue before the meal (provided the meal is not prolonged) should be considered (D).

41. For adults with erratic and unpredictable blood glucose control (hyper- and hypo-glycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:

- **resuspension of insulin and injection technique**
- **injection sites**
- **self-monitoring skills**
- **knowledge and self-management skills**
- **nature of lifestyle**
- **psychological and psychosocial difficulties**
- **possible organic causes such as gastroparesis (D).**

42. Continuous subcutaneous insulin infusion (insulin pump therapy) is recommended as an option for people with Type 1 diabetes provided that:

43. multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed;[a] and

[a] People for whom multiple-dose therapy has failed are considered to be those for whom it has been impossible to maintain an HbA1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self-care of their diabetes. 'Disabling hypoglycaemia', for the purpose of this guidance, means the repeated and unpredicted occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life.

44. those receiving the treatment have the commitment and competence to use the therapy effectively (NICE).

45. Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some meal-time insulin) should be considered for adults starting insulin therapy, until such time as islet B-cell deficiency progresses further (D).

46. Clear guidelines and protocols (`sick day rules') should be given to all adults with Type 1 diabetes to assist them in adjusting insulin doses appropriately during intercurrent illness (D).

47. Oral glucose-lowering drugs should generally not be used in the management of adults with Type 1 diabetes (D).

6.4 Insulin delivery

6.4.1 Rationale

As a large protein, insulin cannot be taken orally (it is digested) and is only absorbed across mucous membranes (of the nose or inside cheeks for example) very poorly. As a result, it generally has to be injected or infused into the subcutaneous fat. Self-use of injection devices is not something most people adopt happily by choice, and since the late 1970s various solutions to making this easier and more satisfactory have been developed.

6.4.2 Evidence statements

NICE guidance concluded that, compared to optimised MDI therapy, CSII results in a modest but worthwhile improvement in GHb and quality of life (by allowing greater flexibility of lifestyle), and reduction of other problems such as hypoglycaemia and rising blood glucose levels at the end of the night.[362] In routine practice, patients who go on to pumps are carefully selected, and to a large degree self-selected. Overall, insulin pumps appear to be a useful advance for patients having particular problems, rather than a dramatic breakthrough in therapy, and would probably be used only in a small percentage of patients (**NICE**).

There is a paucity of trials of sufficient sample size in comparing insulin injection pens to other forms of insulin delivery.

One randomised trial of medium sample size compared a multiple injection regimen from a pen injector with conventional treatment with twice-daily syringe injection.[349] No significant differences were seen in GHb values, blood glucose values or hypoglycaemic episodes. Patient satisfaction with pen injectors was high and most patients opted to continue on this delivery system following termination of the trial. However, this study has some methodological limitations (**Ib**).

One randomised cross-over trial compared two types of insulin regimen injected in the abdomen with the same regimen injected in the thigh.[47] Regular insulin injections in the abdomen resulted in significantly lower post-prandial plasma glucose values, peak plasma glucose and increment in plasma glucose compared to time periods following injection in the thigh. Significantly higher serum free insulin values were also seen following abdominal injection of regular insulin, compared with injections administered at the thigh. No differences were recorded between injections at either site following injections containing both isophane (NPH) and unmodified ('soluble') insulin (**Ib**).

One prospective study comparing the absorption of insulin injected superficially and deep subcutaneously at the fat-muscle boundary showed no significant difference between the two techniques.[119] A sub-group of 10 participants showed no difference in overall serum free insulin or plasma glucose values following superficial and deep subcutaneous injection (**IIa**).

One study reported benefits associated with injection through clothing, compared with conventional injection practice with skin preparation over a 20- week trial period.[151] This study had some methodological limitations (**Ib**).

Outside of the recommendations made on continuous subcutaneous insulin infusion,[361] no studies were identified that specifically addressed the insulin delivery needs of people with Type 1 diabetes with poor blood glucose control.

6.4.3 Health economic evidence

The health economic searches produced three published papers considering the use of insulin pens.[224,235,236] None of the three papers compare their benefits (patient satisfaction, or improved HbA1c) against their costs.

6.4.4 Consideration

Insulin injection pens were noted to be the overwhelming norm in the UK for insulin delivery for reasons of convenience, ease of teaching, and portability. Some devices with particular design characteristics can be used by people with disabilities, where otherwise a third party would have to give injections. The desirability and often cost-effectiveness of this was noted. Injection into deep subcutaneous fat, and on the basis of many studies into the tissues of the abdominal wall for meal-time unmodified human insulin, are generally advised and logically based. However the needs and beliefs of individuals in giving their own insulin were felt to be of importance. Simple logic also leads to the conclusion that rotation of injection sites should be within one region rather than between regions. Group members (both clinicians and patients) expressed a widespread experience of repeated self-injection with the same needle without problems arising. The group considered the utility of recommending advice on cleanliness for those who choose to re-use needles, but noted the regulatory position from the Medicines and Healthcare Products Regulatory Agency (MHRA, formerly the Medical Devices Agency) in the bulletin DB2000(04). Consequently, the guideline cannot make such a recommendation. Other common sense issues included provision for sharps disposal, and check on the condition of injection sites annually or if blood glucose control problems worsen.

6.4.5 Recommendations

48. Insulin injection should be made into the deep subcutaneous fat. To achieve this, needles of a length appropriate to the individual should be made available (D).

49. Adults with Type 1 diabetes should be informed that the abdominal wall is the therapeutic choice for meal-time insulin injections (D).

50. Adults with Type 1 diabetes should be informed that extended-acting suspension insulin (e.g. isophane (NPH) insulin) may give a longer profile of action when injected into the subcutaneous tissue of the thigh rather than the arm or abdominal wall (D).

51. Adults with Type 1 diabetes should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area (D).

52. Injection site condition should be checked annually, and if new problems with blood glucose control occur (D).

6.5 Hypoglycaemia: prevention, problems related to hypoglycaemia, and management of symptomatic hypoglycaemia

Blood glucose awareness training

A randomised controlled study compared blood glucose awareness training (BGAT) with no training on the increased hypoglycaemia after initiation of more intensive diabetes management.[253] The counter-regulatory hormone epinephrine (adrenaline) response was not impaired following BGAT despite an increase in frequency of hypoglycaemia induced by intensive diabetes management. No difference was seen in awareness of the symptoms of hypoglycaemia following BGAT, compared with controls, although BGAT does lead to a better detection of low blood glucose levels in people starting intensive diabetes management (**Ib**).

An observational study compared blood glucose sensitivity and prediction accuracy in in-patients before and after blood glucose awareness training, showed no additional effect on the improvement of HbA1c.[155] The decrease in HbA1c was not however accompanied by a change in the accuracy of blood glucose estimation or sensitivity of recognition of low blood glucose levels (I**Ia**).

Canadian Clinical Practice guidelines, cite five studies demonstrating a positive effect of BGAT on accurate detection and treatment of hypoglycaemia, and allowing reduced-awareness subjects to detect a greater percentage of low blood glucose levels.[531] These BGAT programmes involve instruction in interpretation of physical symptoms and instruction on food, exercise, insulin dosage and action, and the impact of time of day and last blood glucose measurements on estimations of blood glucose (**Ia**).

6.5.1 Recommendations

R74: Adults with Type 1 diabetes should be informed that any available glucose/sucrose containing fluid is suitable for the management of hypoglycaemic symptoms or signs in people who are able to swallow. Glucose containing tablets or gels are also suitable for those able to dissolve or disperse these in the mouth and swallow the products. (**A**)

R75: When a more rapid-acting form of glucose is required, purer glucose-containing solutions should be given. (**D**)

R76: Adults with decreased level of consciousness due to hypoglycaemia who are unable to take oral treatment safely should be:

- given intramuscular glucagon by a trained user; intravenous glucose may be used by professionals skilled in obtaining intravenous access.
- monitored for response at 10 minutes, and then given intravenous glucose if the level of consciousness level is not improving significantly.
- then given oral carbohydrate when it is safe to administer it, and placed under continued observation by a third party who has been warned of the risk of relapse. (**D**)

Hypoglycaemia unawareness should be assumed to be secondary to undetected periods of hypoglycaemia (<3.5 mmol/l, often for extended periods, commonly at night) until these are excluded by appropriate monitoring techniques; if present such periods of hypoglycaemia should be ameliorated. (**D**)

Specific education on the detection and management of hypoglycaemia in adults with problems of hypoglycaemia awareness should be offered. (**D**)

53. Nocturnal hypoglycaemia (symptomatic or detected on monitoring) should be managed by:

- **reviewing knowledge and self-management skills**
- **reviewing current insulin regimen and evening eating habits and previous physical activity**
- **choosing an insulin type and regimen with less propensity to induce low glucose levels in the night hours, such as:**
    - **isophane (NPH) insulin at bedtime**
    - **rapid-acting analogue with the evening meal**
    - **long-acting insulin analogues (glargine)**
    - **insulin pump. (D)**

7 Arterial risk control

7.1 Identification of arterial risk

7.1.1 Recommendations

54. Arterial risk tables, equations or engines for calculation of arterial risk should not be used because they underestimate risk in adults with Type 1 diabetes. (DS)

55. Adults with raised albumin excretion rate (microalbuminuria), or two or more features of the metabolic syndrome (see box), should be managed as the highest risk category (as though they had Type 2 diabetes or declared arterial disease). (D)

Table 111: Features of the metabolic syndrome and arterial risk

Features of the metabolic syndrome suggesting high arterial risk in people with Type 1 diabetes		
	Women	**Men**
Blood pressure average (mmHg)	>135/80	>135/80
Waist circumference (m)	>0.90	>1.00
	Use 0.10 lower figures for people of South Asian extraction	
Serum HDL cholesterol (mmol/l)	<1.2	<1.0
Serum triglycerides (mmol/l)	>1.8	>1.8
Raised albumin excretion rate is not included, because in Type 1 diabetes it is a marker of developing nephropathy, and nephropathy alone is associated with extreme risk of ischeamic heart disease.		
Glucose intolerance cannot be assessed in adults with Type 1 diabetes, but higher insulin doses in adults >20 years (>1.0U/kg/day) suggest insulin insensitivity.		

56. Adults with Type 1 diabetes who are not in the highest risk category but who have other arterial risk factors (increasing age over 35 years, family history of premature heart disease, of ethnic group with high risk, or with more severe abnormalities of blood lipids or blood pressure) should be managed as a moderately high risk group. (D)

57. Where there is no evidence of additional arterial risk, the management of lipids and blood pressure should follow normal procedures for the non-diabetes population, using appropriate clinical guidelines. (D)

7.2 Interventions to reduce risk and to manage arterial disease

7.2.1 Recommendations

These recommendations assume that arterial risk has been assessed according to the recommendations in section 8.1. Blood glucose control, blood pressure control and education programmes are considered elsewhere in this guideline (see 7, 8.3, 6.1 respectively).

58. Aspirin therapy (75 mg daily) should be recommended in adults in the highest and moderately-high risk categories.

59.A standard dose of a statin should be recommended for adults in the highest risk and moderately-high risk groups. Therapy should not be stopped if alanine aminotransferase(ALT) is raised to less than three times the upper limit of reference range.

60.If several statins are not tolerated, fibrates and other lipid-lowering drugs should beconsidered as indicated according to assessed arterial risk status.

61.Fibrates should be recommended for adults with hypertriglyceridaemia according to local lipid-lowering guidelines, and arterial disease risk status.

62.Responses to therapy should be monitored by assessment of lipid profile. If the response is unsatisfactory, the following causes should be considered: non-concordance, inappropriate drug choice and the need for combination therapy.

7.3 Blood pressure

7.3.1 Recommendations

63.

8 Management of late complications: diabetic eye disease

8.1 Retinopathy surveillance programmes

8.1.1 Recommendations

64.Structured eye surveillance should be at one-year intervals.

8.2 Screening tests for retinopathy

(NICE).[370]

8.2.1 Consideration

65.Mydriasis with tropicamide should be used when photographing the retina, after prior agreement with the person with Type 1 diabetes following discussion of the advantages and disadvantages, including appropriate precautions for driving.

66.Visual acuity testing should be a routine part of eye surveillance programmes.

8.3 Referral

8.3.1 Recommendations

67.Emergency review by an ophthalmologist should occur for:

- **sudden loss of vision**
- **rubeosis iridis**
- **pre-retinal or vitreous haemorrhage**
- **retinal detachment.**

68.Rapid review by an ophthalmologist should occur for new vessel formation.

69.Referral to an ophthalmologist should occur for:

- **referable maculopathy:**
- **exudate or retinal thickening within one disc diameter of the centre of the fovea**
- **circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea)**
- **any microaneurysm or haemorrhage within one disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse**
- **referable pre-proliferative retinopathy (if cotton wool spots are present, look carefully for the following features, but cotton wool spots themselves do not define pre-proliferative retinopathy):**

- **any venous beading**
- **any venous loop or reduplication**
- **any intraretinal microvascular abnormalities (IRMA)**
- **multiple deep, round or blot haemorrhages.**
- **any unexplained drop in visual acuity.**

8.4 Management of late complications: diabetic kidney disease

Kidney damage

8.4.1 Recommendations

See also recommendations for blood pressure in section 8.3.

70. All adults with Type 1 diabetes, with or without detected nephropathy, should be asked to bring in a first-pass morning urine specimen once a year. This should be sent for estimation of albumin:creatinine ratio. Estimation of urine albumin concentration alone is a poor alternative. Serum creatinine should be measured at the same time.

71. If an abnormal surveillance result is obtained (in the absence of proteinuria/urinary tract infection), the test should be repeated at each clinic visit or at least every three to four months, and the result taken as confirmed if a further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men, >3.5 mg/mmol for women).

72. If ACE inhibitors are not tolerated, angiotensin 2 receptor antagonists should be substituted. Combination therapy is not recommended at present.

8.5 Management of late complications: diabetes foot problems

Screening and surveillance of diabetic foot problems

8.5.1 Rationale

Foot ulceration, foot infection, foot and limb amputation and some forms of deformity (including Charcot arthropathy) are major forms of disability arising from Type 1 diabetes. Prevention and management of such problems depends on detection of risk factors, and of markers of predisposing problems including neuropathy and vascular disease, as well as more diverse factors such as poor footwear and skin condition. Accurate and programmed surveillance for such risk factors is required if efficient use is to be made of education programmes and the services of those with special expertise in management of individuals with particularly high risk of foot ulceration.

8.5.2 Evidence statements

Monitoring

The major risk factors for foot complications have been identified in several systematic reviews as history of ulceration and lack of sensation.[358,451]

The NICE Clinical guidelines for Type 2 diabetes reported inconsistent evidence of markers associated with foot complications from nine studies using a range of methods and patient data.[358] These included: old age, duration of diabetes, neuropathy, peripheral vascular disease, renal disease, foot deformities, plantar callus, previous ulceration or amputation, poor vision, poor footwear, cigarette smoking, social deprivation and social isolation (NICE).

The NICE guideline also reported five surveys investigating additional risk factors for the elderly, concluded that suboptimal supervision of elderly patients in hospital, residential care and general practice increases their risk of ulceration and amputation (NICE).[358]

Organisation of screening programmes

The SIGN guidelines note that absence of reliable symptoms and the high prevalence of asymptomatic disease make foot screening essential (IV).[451]

One large comparative trial in a systematic review of a combined screening and foot protection programme reported a statistically significant reduction in major amputations over a two-year period compared to normal organisation of care (Ia).[378]

The NICE clinical guidelines report a Cochrane review comparing trials of general practice vs hospital care for recall and review of foot problems, and conclude that despite the methodological flaws in these trials a system of shared care – joint participation between hospitals and general practices – provides levels of surveillance as good as hospital diabetic clinic attendance alone (NICE).[358]

Information exchange between specialists is advocated in one review in the NICE Type 2 diabetes guidelines.[358] However, no evidence exists to specify the components of these procedures (NICE).

The guidelines foot care working party also endorsed the findings of Diabetes UK that a multidisciplinary team of professionals should be available to promptly provide the full range of appropriate foot care services to patients (NICE).[358]

Detection of loss of foot sensation

SIGN guidelines concluded from three studies that neuropathy screening performed by using clinical neuropathy disability scores, 10 g monofilaments or vibration perception thresholds, alone or in combination, have benefits in selecting patients at increased risk of foot ulceration (DS).[451]

Additional techniques available for assessing neuropathic deficit that are considered in SIGN guidelines include tactile circumferential discriminator, the graduated tuning fork, thermal discrimination devices and others.[451] These techniques have not been prospectively evaluated but generally compare with other techniques for detection of ulcers (IV).

There is general agreement in systematic reviews and guidelines that the 5.07 mono- filament (10 g) is cheap and easy to use compared to other neuropathic tests and is the recommended screening test for neuropathy as a risk factor for diabetes foot ulcers (IV/NICE).[358,451]

A systematic review of a particular monofilament and other threshold tests for preventing ulceration and amputation in people with diabetes found this design of monofilament correlated best with the presence or history of an ulcer.[313] Evidence varies as to the appropriate number of sites to use with this technique, the majority of studies testing at ?1 site. The plantar surface of the forefoot provides the best discrimination between those who did and did not have ulcers (III).

Four prospective studies included in a systematic review described a strong predictive ability of the monofilament test for future foot ulceration and amputation and a high reproducibility (DS).[313]

Within a systematic review two non-randomised studies reported physical symptoms of tingling, burning, hyperaesthesia and other uncomfortable sensations affecting >40% of people with diabetes after diagnosis.[313] However, two separate studies reported poor correlation of pain symptoms with foot ulceration (III).

Prospective evidence is sparse for traditional clinical assessment, using pinprick, tuning fork vibration or light touch with a cotton wisp.[313] While the reproducibility of these investigations is low, replicability is slightly better for ankle jerks; however these tests are considered poor predictors of ulceration (DS).

Two-point discrimination was shown in one study in a well-produced systematic review to be more sensitive but less specific than monofilament or vibration perception threshold (VPT) testing.[313] Temperature sensation was found in two studies to be cumbersome and irritating and correlated less well with risk of ulceration compared to monofilament or VPT (DS).

One further medium-sized diagnostic study described the comparability of a new technique combining a monofilament and pinprick test to reference standard tests.[388] The new technique was found to have good correlation with VPT and a neuropathy disability score assessment, and a specificity and sensitivity of roughly 80% and 70% respectively in detecting both neuropathy disability score and VPT results identifying moderate to severe neuropathy (DS).

Detection of peripheral vascular disease

Screening for vascular insufficiency is less well documented than ulceration in existing reviews (IV).[451]

Two studies in the SIGN guidelines note that absence of pedal pulses can be used in first-line screening as a guide to peripheral vascular disease.[451] Evidence from one study urges caution when evaluating ankle pressure and pressure indices, which can be falsely elevated in people with diabetes (DS).

A systematic review of observational studies noted a restricted accuracy of pedal pulses in identifying severe peripheral ischaemia (DS).[64]

The validity of Doppler ultrasonography to determine ankle-branchial index as an indicator of peripheral blood flow was also questioned by one study in a systematic review.[64] The study noted that calcification of the media of the distal arteries, common in diabetes, may lead to artificially high systolic pressure in the ankle (DS).

8.5.3 Health economic evidence

The health economic search found no papers specific to foot care screening or treatment in Type 1 diabetes. As the Type 2 diabetes foot care guideline will use all the information identified in the health economic searches, and may use other information excluded in the search process, the specific health economic recommendations from this guideline should be applied here.

The only exception to this comes in the cost-effectiveness of cultured human dermis where additional modelling was undertaken. Two economic evaluations[30,498] were identified from the literature for Dermagraft, of which one paper used UK cost data,[498] but the results were unpublished. The remaining paper considers French cost-effectiveness in terms of cost per ulcer healed over 52 weeks.[30] This model was replicated by the health economist in the GDG, but its findings could not be duplicated. No conclusion can therefore be drawn from these studies.

This replicated model was used to construct an estimate of the cost-effectiveness of Dermagraft in QALY terms using published health utility values. Dermagraft does not appear to be a cost- effective

treatment for diabetic foot ulcers on the basis of this model. Furthermore, as the clinical data underlying this model relates to long-standing ulcers that may be less likely to heal with standard treatment, the general cost-effectiveness of Dermagraft for all non-recurrent ulcers free of infection is likely to be worse than the figures produced here.

8.5.4 Consideration

The group noted that this area had been examined by other quality guideline groups both internationally and for Type 2 diabetes. No reason for being inconsistent with those recommendations could be found, although for the most part people with foot problems and Type 1 diabetes had predominantly neuropathic problems rather than neuroischaemic problems. Annual foot review was thought desirable for reasons of both foot surveillance and education. The simple and effective utility of the monofilament was noted.

8.5.5 Recommendations

73. Structured foot surveillance should be at one-year intervals, and should include educational assessment and education input commensurate with the assessed risk.

74. The reasons for, and success of, foot surveillance systems should be properly conveyed to adults with Type 1 diabetes, so that attendance is not reduced by ignorance of need.

75. Inspection and examination of feet should include:

- **skin condition**
- **shape and deformity**
- **shoes**
- **impaired sensory nerve function**
- **vascular supply (including peripheral pulses).**

76. Use of a 10 g monofilament plus non-traumatic pin prick is advised for detection of impairment of sensory nerve function sufficient to significantly raise risk of foot ulceration.

8.6 Management of foot ulceration and associated risk factors

8.6.1 Rationale

Diabetes foot problems lead to significant morbidity and healthcare costs from foot ulceration and limb amputation. In Type 1 diabetes the predominant risk factor is the development of somatic sensory neuropathy, although peripheral vascular disease may contribute to the risks in some people. Poor blood glucose control can interfere with healing and control of infection where skin damage occurs.

8.6.2 Evidence statements

There were no randomised controlled trials identified from the search of interventions for managing foot ulceration and infection in populations with Type 1 diabetes specifically. We therefore recommend following the Type 2 diabetes guideline for foot care, which considered evidence from trials with populations with Type 2 diabetes, and mixed Type 1 and Type 2 diabetes (www.nice.org.uk) (NICE).

8.6.3 Consideration

The group noted the draft recommendations of the updated Type 2 diabetes foot care guideline, and the differences between Type 1 and Type 2 diabetes in respect of this area, mainly arising as a result of the lesser impact of peripheral vascular disease in people with Type 1 diabetes. The importance of trained foot care personnel was noted from the evidence statements in chapter 5. Disappointingly there was little evidence on the effectiveness of the different antibiotic regimens employed. The sometimes rapid progression from the start of ulceration to cellulitis was felt to justify very rapid referral and review by a specialist team where ulceration is detected.

The economic analysis provided to the group was felt to be secure in suggesting that human cultured dermis was not a cost-effective option in the context of the current NHS.

At the time of review by the group the evidence on Charcot osteoarthropathy management was felt to be incomplete, and the group did not reach any conclusions on the subject. A recommendation was based on the draft of the updated NICE guideline on foot care in Type 2 diabetes.

8.6.4 Recommendations

Foot complication surveillance

77. On the basis of findings from foot care surveillance, foot ulceration risk should be categorised into:

- **low current risk (normal sensation and palpable pulses)**
- **increased risk (impaired sensory nerve function or absent pulses, or other risk factor)**
- **high risk (impaired sensory nerve function and absent pulses or deformity or skin changes, or previous ulcer)**
- **ulcer present.**

Foot care management

78. For people found to be at increased risk or high risk of foot complications:

- **arrange specific assessment of other contributory risk factors including deformity, smoking, level of blood glucose control**
- **arrange/reinforce specific foot care education, and review those at high risk as part of a formal foot ulcer prevention programme**
- **consider the provision of special footwear, including insoles and orthoses, if there is a deformity, callosities or previous ulcer.**

79. For people with an ulcerated foot:

- **arrange referral to a specialist diabetes foot care team incorporating specifically- trained foot care specialists (usually state-registered podiatrists) within one to two days if there is no overt infection of the ulcer or surrounding tissues, or as an emergency if such infection is present**
- **use antibiotics if there is any evidence of infection of the ulcer or surrounding tissues, and continue these long-term if infection is recurrent**
- **use foot dressings taking account of cost according to local experience, ensuring arrangements are in place to monitor and change dressings frequently (often daily) accordingly to need**

- **remove dead tissue from diabetic foot ulcers**
- **consider the use of off-loading techniques (such as contact casting) for people with neuropathic foot ulcers**
- **do not use cultured human dermis (or equivalent), hyperbaric oxygen therapy, topical ketanserin or growth factors in routine foot ulcer management**
- **consider ensuring complete and effective foot education through the use of graphic visualisations of the consequences of ill-managed foot ulceration in people with recurrent ulceration or previous amputation**
- **review progress in ulcer healing frequently (daily to monthly) according to need**
- **if peripheral vascular disease is detected, refer for early assessment by a specialist vascular team.**

Charcot osteoarthropathy

80. Adults with suspected or diagnosed Charcot osteoarthropathy should be referred immediately to a multidisciplinary diabetes foot care team.

8.7 Management of late complications: diabetes nerve damage

Diagnosis and management of erectile dysfunction

8.7.1 Rationale

Erectile dysfunction in men with diabetes is common, and to a greater extent than in the matched general population. There is some debate as to whether professionals should actively ask about erectile problems on a recurrent basis (perhaps yearly), or only respond to self- reported problems. There have been dramatic changes in the approach to male erectile dysfunction in recent years, stimulated by the advent of the phosphodiesterase type 5 (PDE5) inhibitors.

8.7.2 Evidence statements

Significance of patient-reported sexual symptomatology in predicting actual physiological measures of sexual dysfunction

A medium-sized cross-sectional cohort study in people with diabetes mellitus evaluated the significance of patient-reported sexual symptomatology in predicting penile tip and base rigidity, tip and base duration of erectile episode.[21] This study reports that the presence of morning erections was associated with increased Rigiscan values of tip rigidity (r=0.64), base rigidity (r=0.58), tip duration of erectile episode (r=0.65) and base duration of erectile episodes (r=0.57), all demonstrating significant relationships (IIa).

Reports of fuller erectile quality were also significantly associated with increased Rigiscan values of tip rigidity (r=0.58), base rigidity (r=0.42), tip duration of erectile episode (r=0.67) and base duration of erectile episode (r=0.71).249 Other significant associations found in this cohort study included intact ejaculatory capacity being associated with increased Rigiscan measures of tip rigidity (r=0.45). Tip duration of erectile episode (r=0.56) and base duration of erectile episode (r=0.30) were also related to Rigiscan measures in the same study.[21]

A significant inverse relationship was found between symptom frequency and the Rigiscan measure of base duration of erectile episodes, with greater symptom frequency being associated with diminished duration values of erectile episodes at the penile base (r=-0.39) (IIa).[21]

Correlations of lower limb nerve fibre abnormalities with erectile dysfunction

A medium-sized cross-sectional cohort study aimed to characterise the neuropathy in erectile dysfunction, as well as to identify nerve fibre subtypes that may be preferentially affected.[516] Patients were evaluated with a symptom questionnaire based on the Michigan Neuropathy Screening instrument questionnaire and examined clinically. Sural and peroneal nerve-conduction studies and quantitative sensory and autonomic tests (using the staging system of Dyck) were used to detect nerve abnormalities in the lower limbs. Various methodological limitations inherent to the study limited the validity of the results derived from the trial (IIa).

Relationship of symptoms of depression, sexual dysfunction and neuropathy in women

A small cross-sectional cohort study assessed the relationship between symptoms of depression (as measured by the Beck Depression Inventory and the Hamilton Psychiatric Rating Scale), sexual dysfunction (as measured by a questionnaire which asked patients to rate their symptoms on a scale from 0 to 10), and neuropathy (as measured by the visual analogue scale).[284] However, various methodological limitations inherent to the study limit the validity of the results derived from the trial, and should not be used as the basis for a positive recommendation (IIa).

Sildenafil

One large multicentre study of sildenafil at 100 mg/day compared to placebo in men with erectile dysfunction and Type 1 or Type 2 diabetes found significantly more men were able to achieve and to maintain erections with sildenafil than placebo at 12 weeks.[50] Another 11 outcomes from questionnaire-based evaluation of male sexual function described significant improvement with the intervention drug, however there were no differences in indices of frequency and level of sexual desire. Erectile function was improved regardless of age, duration of erectile dysfunction, duration of diabetes or type of diabetes, and the incidence of adverse arterial events was similar in both groups (Ib).

A smaller prospective study from the UK found that sildenafil at 25 mg or 50 mg, compared to placebo, significantly improved adjusted duration of penile rigidity at base and tip.[411] In addition, there was an improved number of erections hard enough for sexual intercourse with either dose, with no serious adverse events being related to treatment (Ib).

8.7.3 Consideration

The group noted the problems surrounding asking all men about impotence, but suggested a reasonable approach to this problem is to enquire as to whether individuals were 'troubled by sexual dysfunction'. It was not felt that the current opportunities for assisting women with problems of organic sexual dysfunction secondary to diabetes could justify routine enquiry. The group noted the licensing in 2003 of two additional PDE5 inhibitors to sildenafil, and felt that the lack of comparative trials meant that any recommendations should be for the drug class rather than any individual agent. Men still having a problem after a trial of PDE5 inhibitors had failed might have their needs met by expertise available in a variety of care situations, suggesting that the site of such care and advice could not be specified.

8.7.4 Recommendations

81. Men should be asked annually whether erectile dysfunction is an issue.

82. A PDE5 (phosphodiesterase-5) inhibitor drug, if not contraindicated, should be offered where erectile dysfunction is a problem.

83. Referral to a service offering other medical and surgical management of erectile dysfunction should be discussed where PDE5 inhibitors are not successful.

8.8 Diagnosis and management of autonomic neuropathy

8.8.1 Recommendations

84. In adults with Type 1 diabetes on insulin therapy who have erratic blood glucose control (or unexplained bloating or vomiting), the diagnosis of gastroparesis should be considered.

85. In adults with Type 1 diabetes who have altered perception of hypoglycaemia the possibility of sympathetic nervous system damage as a contributory factor should be considered.

86. The management of the symptoms of autonomic neuropathy should include standard interventions for the manifestations encountered (for example, for erectile dysfunction or abnormal sweating).

87. For adults with Type 1 diabetes with diagnosed or suspected gastroparesis a trial of prokinetic drugs is indicated (metoclopramide or domperidone, with cisapride as third line if necessary).

8.9 Optimum management of painful neuropathy

8.9.1 Rationale

Symptomatic neuropathy is unusual amongst the forms of diabetes tissue damage in that it is a relatively early manifestation of the effects of hyperglycaemia, which may go into remission with progression of nerve damage (nerve death) or recovery of nerve fibre function. The symptoms are protean in nature, and often very troublesome to the person with diabetes, especially if sleep is disturbed. Management can be difficult.

8.9.2 Evidence statements

Anticonvulsants

One large meta-analysis found a significant benefit of at least 50% pain relief with people with anticonvulsants compared to placebo.[93] The relative risk estimates showed that anti- convulsants had a significantly increased incidence of adverse effects compared with placebo for minor but not major harm (Ia).

One small, randomised controlled trial of gabapentin found an improvement over placebo control on a pain questionnaire at 12 weeks but with no significant improvement on a visual analogue pain scale, or present pain intensity.[179] No significant adverse events were reported in either study arm but minor events drowsiness, fatigue and imbalance were more common in the population on gabapentin than on placebo (Ib).

The differences in mean pain intensities between the intervention and control groups were significant after eight weeks at lamotrigine doses of 200, 300 and 400 mg in a small-scale prospective randomised trial.[138] This study found no significant changes in assessment of McGill Pain Questionnaire, Beck Depression Inventory and Pain Disability Index (Ib).

Antidepressants

One large meta-analysis found a significant benefit of at least 50% pain relief with people with antidepressants compared to placebo with pooled analyses of tricyclic antidepressants showing significant benefit but no benefit with selective serotonin re-uptake inhibitors.[93]

Tricyclic antidepressants used were prescribed in doses in the low to moderate range for depression. Antidepressants had a significantly increased incidence of adverse effects compared with placebo with typical antimuscarinic effects of dry mouth, constipation and blurred vision. Also major events (leading to withdrawal from the trial) were more common with antidepressants than placebo, the number needed to harm (NNH) for a major adverse effect with antidepressants compared with placebo was 17 (Ia).

A small short-term randomised controlled trial investigating mean pain intensity diary scores in a six-week within-patient comparison, showed that desipramine was superior to placebo.[312] No significant difference between incidence of adverse events or withdrawals between desipramine and placebo groups (Ib).

Other therapies

Amantadine: A small randomised controlled trial with a one-week follow-up found amantadine infusion at 200 mg in 500 ml 0.9% saline infusion over three-hour period caused a significant clinically relevant reduction in pain score when compared with placebo, and caused a significant improvement in the neuropathy symptom score.[35] Following amantadine, there was a clinically significant subjective tenfold improvement in pain relief (Ib).

Capsaicin: A meta-analysis comparing a range of studies with outcomes from four to eight weeks found capsaicin cream produced significantly higher response rates than placebo cream for physician assessment of global pain in two of the trials, but not in the other two (Ia).[538]

Clonidine: No statistically significant difference between intervention and control groups in patients' pain record diary or pain intensity levels in two randomised trials of clonidine.[72,537] In the patients completing the study, dry mouth and drowsiness tended to occur more commonly with clonidine than placebo (Ib).[537]

Gamma-linolenic acid: Compared with placebo, dietary supplementation with gamma- linolenic acid was reported as being associated with significant clinical, neuropsychological and quantitative sensory improvement in established distal diabetic polyneuropathy in the medium term.[231] A significant improvement in the gamma-linolenic acid group compared with the placebo group was seen in nine variables: symptom scores, median MCV (m/s), peroneal MCV (m/s), median CMAP (mV), peroneal CMAP (mV), median SNAP (μV), sural SNAP (μV), ankle HT (°C), wrist HT (°C). This study recruited only people with Type 2 diabetes (Ib).

A second trial confirms this with gamma-linolenic acid being significantly superior in improving neuropsychological, neurological and thermal sensation parameters of diabetic neuropathy compared with placebo over a one-year period.[245] A significant improvement in the gamma-linolenic acid group compared with the placebo group was seen in: peroneal MNCV, median MNCV, extensor digitorium brevis CMAP, thenar CMAP, sural SNAP, median SNAP, wrist heat threshold, wrist cold threshold, arm muscle strength, arm tendon reflexes, leg tendon reflexes, arm sensation, leg sensation. Subgroup analysis showed improvement of outcome parameters with the gamma-linolenic acid was greater in patients with initial HbA1c <10% than those with HbA1c >10% (Ib).

Isosorbide dinitrate (ISDN): A small crossover trial showed significant reductions in pain and burning sensation using the ISDN spray compared with placebo.[535] During the ISDN phase of the study, two patients developed mild transient headaches, which resolved spontaneously and did not affect overall adherence with the spray (Ib).

Mexiletine: Trials of mexiletine have provided mixed results in terms of efficacy for pain reduction in people with diabetes and painful neuropathy. This difference in effect could be due to clinical differences in study populations, doses utilised or length of follow-up measured (Ib).

A significant reduction in pain during night-time (as estimated by the visual analogue scale score for pain) was observed in the mexiletine 675 mg group compared with the placebo group as was a significant reduction in sleep disturbances in a large multicentre randomised trial.[384] No significant difference between groups in daytime pain or global assessment of efficacy was recorded. However, another study showed no improvement in the McGill Questionnaire or on the visual analogue scale for pain to five weeks (Ib).[479]

In contrast a study of mexiletine compared to placebo for 26 weeks found that the Five Item Symptom Scale Score was improved in all but one patient during treatment with mexiletine, but in only two patients during the placebo phase.[342] Mexiletine significantly improved pain, dysaesthesia and paraesthesia. During treatment with mexiletine the visual analogue score fell significantly. Three patients had mild side effects when treated with mexiletine, including nausea, hiccough and tremor (Ib).

Tramadol: A medium-scaled prospective randomised trial of tramadol at up to 200 mg/day found that by day 14 people in the tramadol group had less pain than patients in the placebo group.[198] This benefit lasted through to the end of the trial at day 42. They also scored better on outcomes of physical and social functioning. No statistically significant differences between treatments were noted for current health perception, psychological distress, overall role functioning and the two overall sleep problem indexes and sleep subscales. The most common adverse events in the tramadol group were nausea (23%), constipation (22%), headache (17%) and somnolence (12%). Nine patients treated with tramadol and one treated with placebo discontinued due to adverse events. The most common adverse events leading to discon- tinuation of tramadol were nausea and dyspepsia. However, this study recruited only people with Type 2 diabetes (Ib).

8.9.3 Consideration

The group noted that the severity of neuropathic symptoms varied considerably between individuals. Many of the well-established drugs were used outside licensed indications in contrast to the newest drugs. Established clinical practice, as in most areas of pain control, uses a stepped approach, and no reason for challenging that was found. Nevertheless, the group was also aware that prescribing habits and long review intervals could lead to suboptimal management where therapies proved ineffective, both through a failure to recognise an unsuccessful trial of therapy and through over-slow dose titration. In the absence of comparative studies, while gabapentin was believed more effective than tricyclic drugs, the need for dose titration and problems of intolerance together with

cost suggested the older drugs to be worth a trial first. Other drugs were now felt by the group to be reserved for people failing trials of tricyclic drugs and gabapentin. The group were aware of difficulties with evidence on gamma-linolenic acid, which meant that it could not be considered further for this guideline. The group also noted the availability of local pain management teams for people whose pain does not respond to conventional measures.

8.9.4 Recommendations

88. Where initial measures fail, a low to medium dose of a tricyclic drug should be used, timed to be taken before the time of day the symptoms are troublesome; adults with Type 1 diabetes should be advised that this is a trial of therapy.

89. Where an adequate trial of tricyclic drugs fails, a trial of gabapentin should be started, and not stopped unless ineffective at the maximum tolerated dose or at least 1,800 mg per day.

90. If treatment with gabapentin is unsuccessful, carbamazepine and phenytoin should be considered.

91. Where severe chronic pain persists despite trials of other measures, opiate analgesia may be considered. At this stage the assistance of the local chronic pain management service should be sought.

92. Professionals should be alert to the psychological consequences of chronic painful neuropathy, and offer appropriate management where they are identified.

93. Where drug therapy is successful in alleviating symptoms, trials of reduced dosage and cessation of therapy should be considered after six months of treatment.

94. Where neuropathic symptoms cannot be adequately controlled it is useful, to help individuals cope, to explain:

- **the reasons for the problem**
- **the likelihood of remission in the medium term**
- **the role of improved blood glucose control.**

8.10 Management of special situations

8.10.1 Recommendations

95.

8.11 Diabetic ketoacidosis

8.11.1 Recommendations

96.

97. Bicarbonate should not generally be used in the management of DKA. A

98.

99. In the management of DKA, once plasma glucose concentration has fallen to

100. To reduce the risk of catastrophic outcomes in DKA, monitoring should be continuous and review should cover all aspects of clinical management at frequent intervals.

8.12 Inpatient management

8.12.1 Recommendations

101. From the time of admission, the person with Type 1 diabetes and the team caring for him or her should receive, on a continuing basis, advice from a trained multidisciplinary team with expertise in diabetes.

102. Throughout the course of an inpatient admission, the personal expertise of adults with Type 1 diabetes (in managing their own diabetes) should be respected and routinely integrated into ward-based blood glucose monitoring and insulin delivery, using the person with Type 1 diabetes' own system. This should be incorporated into the nursing care plan.

103. Hospitals should ensure the existence and deployment of an approved protocol for inpatient procedures and surgical operations for adults with Type 1 diabetes. This should aim to ensure the maintenance of near-normoglycaemia without risk of acute decompensation, usually by the use of regular quality-assured blood glucose testing driving the adjustment of intravenous insulin delivery.

Management during acute arterial events

104. Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, should be provided to all adults with Type 1 diabetes with threatened or actual myocardial infarction or stroke. Critical care and emergency departments should have a protocol for such management.

8.13 Psychological problems

8.13.1 Recommendations

105. Diabetes professionals should ensure they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds. They should be familiar with appropriate counselling techniques and appropriate drug therapy, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with well-being or diabetes self-management.

106. Special management techniques or treatment for non-severe psychological illness should not commonly be used, except where diabetes-related arterial complications give rise to special precautions over drug therapy.

8.14 Eating disorders

8.14.1 Recommendations

107. Members of multidisciplinary professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with Type 1 diabetes with:

- **over-concern with body shape and weight**
- **low body mass index**
- **poor overall blood glucose control.**

Appendix T: Changes to recommendations from 2004 guideline

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
1	Diabetes should be confirmed by a single diagnostic laboratory glucose measurement in the presence of classical symptoms, or by further laboratory glucose measurement. The diagnosis may be supported by a raised HbA1c.	Delete.	This recommendation has been deleted because it is not appropriate for type 1 diabetes. It refers to blood tests for which you need to wait for the result, and therefore implies that it is acceptable to wait for HbA1c or laboratory glucose results. This poses a risk to patients as treatment is delayed.
2	Where diabetes is diagnosed, but type 2 diabetes is suspected, the diagnosis of type 1 diabetes should be considered if: • ketonuria is detected, or • weight loss is marked, or • the person does not have features of the metabolic syndrome or other contributing illness.	Updated.	Replaced by: Diagnose type 1 diabetes on clinical grounds in adults presenting with hyperglycaemia, bearing in mind that people with type 1 diabetes typically (but not always) have one or more of: • ketosis • rapid weight loss • age of onset below 50 years • BMI below 25 kg/m^2 • personal and/or family history of autoimmune disease. **[new 2015]** [recommendation 1]
3	When diabetes is diagnosed in a younger person, the possibility that the diabetes is not type 1 diabetes should be considered if they are obese of have a family history of diabetes, particularly if they are of non-white ethnicity.	Delete.	This recommendation has been deleted because retaining it would be dangerous. Readers are more likely to miss the diagnosis of type 1 diagnosis in a person who is black, has a family history or is obese. This recommendation is more relevant to type 2 diabetes.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
4	Tests to detect specific auto-antibodies or to measure C-peptide deficiency should not be regularly used to confirm the diagnosis of type 1 diabetes. Their use should be considered if predicting the rate of decline of islet B-cell function would be useful in discriminating type 1 from type 2 diabetes.	Updated.	Replaced by: Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. **[new 2015]** [recommendation 3]
37	Each adult with type 1 diabetes should be managed as an individual, rather than as a member of any cultural, economic or health-affected group. Attention should be paid to the recommendations given elsewhere in this guideline with respect to the cultural preferences of individual adults with type 1 diabetes.	Regard each adult with type 1 diabetes as an individual, rather than as a member of any cultural, economic or health-affected group (see also recommendations 22, 30 and 65 about the cultural preferences of individual adults with type 1 diabetes). **[2004, amended 2015]** (recommendation 34)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
7	An individual care plan should be set up and reviewed annually, modified according to changes in wishes, circumstances and medical findings, and the details recorded. The plan should include aspects of: • diabetes education including nutritional advice (see 'Approach to education', Section 1.8.1, and 'Dietary management', Section 1.8.3) • insulin therapy (see 'Insulin regimens', Section 1.9.3, and 'Insulin delivery', Section 1.9.4) • self-monitoring (see 'Self-monitoring of glucose', Section 1.8.2) • arterial risk factor surveillance and management (see 'Control of arterial risk', Section 1.10) • late complications surveillance and management (see 'Identification and management of complications', Section 1.11) • means and frequency of communication with the professional care team	Set up an individual care plan jointly agreed with the adult with type 1 diabetes, review it annually and modify it taking into account changes in the person's wishes, circumstances and medical findings, and record the details. The plan should include aspects of: • diabetes education, including nutritional advice (see sections 1.3 and 1.4) • insulin therapy, including dose adjustment (see sections 1.8 and 1.9) • self-monitoring (see section 1.6) • avoiding hypoglycaemia and maintaining awareness of hypoglycaemia • for women of childbearing potential, family planning, contraception and pregnancy planning • arterial risk factor surveillance and management (see section 1.13) • complications surveillance and management	The word 'late' has been deleted (with respect to complications) because it implies advanced complications and takes the focus away from prevention. Some crucial aspects of a care plan have been added for completeness as they were not covered in the 2004 recommendation.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	• follow-up consultations including next annual review. (1.7.1.4)	(see section 1.14) • means and frequency of communicating with the diabetes professional team • follow-up consultations, including frequency of review of HbA1c levels and experience of hypoglycaemia, and next annual review. **[2004, amended 2015]** (recommendation 8)	
9	Conventional technology (telephones), or newer technologies for high-density data transmission of images, should be used to improve process and outcomes.	Delete.	It is outdated and no longer valid.
10	The multidisciplinary team approach should be available to in-patients with diabetes, regardless of the reason for admission (see 'Hospital admission and intercurrent disease', section 1.12.3).	The multidisciplinary team approach should be available to inpatients with type 1 diabetes, regardless of the reason for admission (see section 1.14). **[2004]** (recommendation 10)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
11	At the time of diagnosis and periodically thereafter, adults with diabetes should be offered up-to-date information on the existence of and means of contacting diabetes support groups (local and national), and the benefits of membership.	At the time of diagnosis and periodically thereafter, provide adults with type 1 diabetes with up-to-date information about diabetes support groups (local and national), how to contact them and the benefits of membership. **[2004]** (recommendation 11)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
12	A programme of structured diabetes education covering all major aspects of diabetes self-care and the reasons for it should be made available to all adults with type 1 diabetes in the months after diagnosis, and periodically thereafter according to agreed need following yearly assessment.	Delete.	Replaced by: Offer all adults with type 1 diabetes a structured education of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6-12 months after diagnosis, at a time that is clinically appropriate and suitable for the person. [recommendation 12]
13	Education programmes for adults with type 1 diabetes should be flexible so that they can be adapted to specific educational, social and cultural needs. These	Delete.	Replaced by: Ensure that any structured education

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	needs should be integrated with individual health needs as dictated by the impact of diabetes and other relevant health conditions on the individual.		programme for adults with type 1 diabetes includes the following components: • It is evidence-based, and suits the needs of the person. • It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes. • It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down. • It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme. • It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency. • The outcomes are audited regularly. [recommendation 15]
14	Education programmes for adults with type 1 diabetes should be designed and delivered by members of the multidisciplinary diabetes team in accordance with the principles of adult education.	Delete.	Replaced by: Ensure that any structured education programme for adults with type 1 diabetes includes the following components: • It is evidence-based, and suits the needs of the person. • It has specific aims and learning objectives, and supports the person and

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes. • It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down. • It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme. • It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency. • The outcomes are audited regularly. [recommendation 15]
15	Education programmes for adults with type 1 diabetes should include modules designed to empower adults to participate in their own healthcare through: • enabling them to make judgements and choices about how they effect that care • obtaining appropriate input from the professionals available to advise them.	Delete.	Replaced by: Ensure that any structured education programme for adults with type 1 diabetes includes the following components: • It is evidence-based, and suits the needs of the person. • It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes. • It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			materials, and is written down. • It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme. • It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency. • The outcomes are audited regularly. [recommendation 15]
16	Professionals engaged in the delivery of diabetes care should consider incorporating educational interchange at all opportunities when in contact with a person with type 1 diabetes. The professional should have the skills and training to make best use of such time.	Delete.	Replaced by: Provide information about type 1 diabetes and its management to adults with type 1 diabetes at all opportunities from diagnosis onwards. Follow the principles in the NICE guideline on patient experience in adult NHS services. [recommendation 16]
17	More formal review of self-care and needs should be made annually in all adults with type 1 diabetes, and the agenda addressed each year should vary according to the priorities agreed between the healthcare professional and the person with type 1 diabetes.	Carry out more formal review of self-care and needs annually in all adults with type 1 diabetes. Vary the agenda addressed each year according to the priorities agreed between the healthcare professional and the adult with type 1 diabetes. **[2004, amended 2015]** (recommendation 18)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
18	Self-monitoring of blood glucose levels should be used as part of an integrated package that includes appropriate insulin regimens and education to help choice and achievement of optimal diabetes outcomes.	Delete.	Replaced by: Educate adults with type 1 diabetes about how to measure their blood glucose level, interpret the results and know what action to take. [recommendation 55]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			Support adults with type 1 diabetes to make the best use of data from self-monitoring of blood glucose through structured education (see recommendations 12 and 14). [49]
19	Self-monitoring skills should be taught close to the time of diagnosis and initiation of insulin therapy.	Teach self-monitoring skills at the time of diagnosis and initiation of insulin therapy. **[2004, amended 2015]** (recommendation 50)	The GDG stated that it is important that self-monitoring skills are taught as soon as type 1 diabetes is diagnosed.
20	Self-monitoring results should be interpreted in light of clinically significant life events.	Delete.	Replaced by: Support adults with type 1 diabetes to make the best use of data from self-monitoring of blood glucose through structured educations (see recommendations 12 and 14). [49]
21	Self-monitoring should be performed using meters and strips chosen by adults with diabetes to suit their needs, and usually with low blood requirements, fast analysis times and integral memories.	Delete.	This recommendation has been deleted because it is no longer relevant. Technology for blood glucose meters has advanced since 2004. All blood glucose meters have integrated memories and fast analysis times.
22	Structured assessment of self-monitoring skills, the quality and use made of the results obtained and the equipment used should be made annually. Self-monitoring skills should be reviewed as part of annual review, or more frequently according to need, and reinforced where appropriate.	Carry out a structured assessment annually of self-monitoring skills, the quality and use made of the results obtained and the equipment used. Review self-monitoring skills as part of annual review, or more frequently according to need, and reinforce them where appropriate. **[2004, amended 2015]** (recommendation 51)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
23	Adults with type 1 diabetes should be advised that the optimal frequency of self monitoring will depend on: • the characteristics of an individual's blood glucose	Delete.	Replaced by: Advise routine self-monitoring of blood glucose levels for all adults with type 1

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	control • the insulin treatment regimen • personal preference in using the results to achieve the desired lifestyle.		diabetes, and recommend testing at least 4 times a day, including before each meal and before bed. [recommendation 44]
24	Adults with type 1 diabetes should be advised that the optimal targets for short-term glycaemic control are: • a pre-prandial blood glucose level of 4.0–7.0 mmol/litre and • a post-prandial blood glucose level of less than 9.0 mmol/litre.	Delete.	Replaced by: Advise adults with type 1 diabetes to aim for: • a fasting plasma glucose level of 5–7 mmol/litre on waking and • a plasma glucose level of 4–7 mmol/litre before meals at other times of the day. [recommendation 47]
25	Monitoring using sites other than the fingertips (often the forearm, using meters that require small volumes of blood and devices to obtain those small volumes) cannot be recommended as a routine alternative to conventional self-blood glucose monitoring.	Monitoring blood glucose using sites other than the fingertips cannot be recommended as a routine alternative to conventional self-monitoring of blood glucose. **[2004, amended 2015]** (recommendation 54)	Blood glucose has been stated for clarity. The statements about small volumes and special devices for alternative site monitoring have been removed because (1) the 2015 guideline supports the 2004 view that alternative site monitoring is not recommended, so the comment is redundant and (2) all meters now use small volumes.
27	Nutritional information should be offered individually and as part of a diabetes education programme (see education recommendations in section 1.8.1). Information should include advice from professionals with specific and approved training and continuing accredited education in delivering nutritional advice to people with health conditions. Opportunities to receive nutritional advice should be offered at intervals agreed between adults with diabetes and their advising professionals.	Provide nutritional information individually and as part of a diabetes education programme (see section 1.3). Include advice from professionals with specific and approved training and continuing accredited education in delivering nutritional advice to people with health conditions. Offer opportunities to receive nutritional advice at intervals agreed between adults with type 1 diabetes and their advising professionals. **[2004]** (recommendation 22)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
29	Programmes should be available to adults with type 1	Make programmes available to adults with type 1	NICE has made editorial changes to the

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	diabetes to enable them to make: • optimal choices about the variety of foods they wish to consume • insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods.	diabetes to enable them to make: • optimal choices about the variety of foods they wish to consume • insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods. **[2004, amended 2015]** (recommendation 25)	original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
31	Information should also be made available on: • effects of different alcohol-containing drinks on blood glucose excursions and calorie intake • use of high-calorie and high-sugar 'treats' • use of foods of high glycaemic index.	Make information available on: • effects of different alcohol-containing drinks on blood glucose excursions and calorie intake • use of high-calorie and high-sugar 'treats'. **[2004, amended 2015]** (recommendation 27)	There is no evidence of benefit for a low glycaemic index diet (see recommendation 21), so the reference to giving information about foods of high glycaemic index has been deleted.
32	Information about the benefits of healthy eating in reducing arterial risk should be made available as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. This should include information about low glycaemic index foods, fruit and vegetables, and types and amounts of fat, and ways of making the appropriate nutritional changes.	Make information available about the benefits of healthy eating in reducing arterial risk as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. Include information about fruit and vegetables, types and amounts of fat, and ways of making the appropriate nutritional changes. **[2004, amended 2015]** (recommendation 28)	There is no evidence of benefit for a low glycaemic index diet (see recommendation 21), so the reference about giving information about foods of low glycaemic index has been deleted.
34	All healthcare professionals providing advice on the management of type 1 diabetes should be aware of appropriate nutritional advice on common topics of concern and interest to adults living with type 1 diabetes, and should be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include: • glycaemic index of specific foods • body weight, energy balance and obesity management • cultural and religious diets, feasts and fasts	Be aware of appropriate nutritional advice on common topics of concern and interest to adults living with type 1 diabetes, and be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include: • body weight, energy balance and obesity management • cultural and religious diets, feasts and fasts • foods sold as 'diabetic' • sweeteners	There is no evidence of benefit for a low glycaemic index diet (see recommendation 21), so the reference about giving information about the glycaemic index of foods has been deleted.

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	• foods sold as 'diabetic' • sweeteners • dietary fibre intake • protein intake • vitamin and mineral supplements • alcohol • matching carbohydrate, insulin and physical activity • salt intake in hypertension • co-morbidities including nephropathy and renal failure, • coeliac disease, cystic fibrosis or eating disorders • use of peer support groups.	• dietary fibre intake • protein intake • vitamin and mineral supplements • alcohol • matching carbohydrate, insulin and physical activity • salt intake in hypertension • comorbidities, including nephropathy and renal failure, coeliac disease, cystic fibrosis or eating disorders • use of peer support groups. **[2004, amended 2015]** (recommendation 29)	
38	Clinical monitoring of blood glucose levels by high-precision DCCT-aligned methods of haemoglobin A1c (HbA1c) should be performed every 2-6 months, depending on: • achieved level of blood glucose control • stability of blood glucose control • change in insulin dose or regimen.	Delete.	Replaced by: Measure HbA1c levels every 3–6 months in adults with type 1 diabetes. [recommendation 35]
39	Site-of-care measurement, or before-clinical-consultation measurement, should be provided.	Delete.	Replaced by: Inform adults with type 1 diabetes of their HbA1c results after each measurement and ensure that their most recent result is available at the time of consultation. Follow the principles in the NICE guideline on patient experience in adult NHS services about communication. [recommendation 38]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
40	HbA1c results should be communicated to the person with type 1 diabetes after each measurement. The term A1c can be sued for simplicity.	Delete.	Replaced by: Inform adults with type 1 diabetes of their HbA1c results after each measurement and ensure that their most recent result is available at the time of consultation. Follow the principles in the NICE guideline on patient experience in adult NHS services about communication. [recommendation 38]
41	Total glycated haemoglobin estimation, or assessment of glucose profiles, should be used where haemoglobinopathy or haemoglobin turnover invalidate HbA1c measurement. (1.9.1.4)	If HbA1c monitoring is invalid (because of disturbed erythrocyte turnover or abnormal haemoglobin type), estimate trends in blood glucose control using one of the following: • fructosamine estimation • quality-controlled blood glucose profiles • total glycated haemoglobin estimation (if abnormal haemoglobins). **[2004, amended 2015]** (recommendation 43)	The GDG agreed to adopt the recommendation on this topic from the NICE guideline on type 2 diabetes.
42	Fructosamine should not be used as a routine substitute for HbA1c estimation.	Delete.	This recommendation has been deleted because it is redundant. Clinical practice has changed. Now it is clinical practice to use HbA1c, whereas in 2004 there was a mixture of both methods.
43	Continuous glucose monitoring systems have a role in the assessment of glucose profiles in adults with consistent glucose control problems on insulin therapy, notably: • repeated hyper- or hypoglycaemia at the same time of day • hypoglycaemia unawareness, unresponsive to conventional insulin and dose adjustment.	Delete.	Replaced by: Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following that persist despite optimised use of insulin therapy and conventional

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			blood glucose monitoring: • more than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause • complete loss of awareness of hypoglycaemia • frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities • extreme fear of hypoglycaemia. [recommendation 57]
44	Adults with type 1 diabetes should be advised that maintaining a DCCT harmonised HbA1c below 7.5% is likely to minimise their risk of developing diabetic eye, kidney or nerve damage in the longer term.	Delete.	Replaced by: Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [recommendation 39]
45	Adults with diabetes who want to achieve an HbA1c down to, or towards, 7.5% should be given all appropriate support in their efforts to do so.	Delete.	Replaced by: Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [recommendation 39]
46	Where there is evidence of increased arterial risk (identified by a raised albumin excretion rate, features of the metabolic syndrome, or other arterial risk factors), people with type 1 diabetes should be advised that approaching lower HbA1c levels (for example, 6.5% or lower) may be of benefit to them. Support should be given to approaching this target if so wished.	Delete.	Replaced by: Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [recommendation 39] Agree an individualised HbA1c target with each adult with type 1 diabetes, taking

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. [recommendation 40]
48	Undetected hypoglycaemia and an attendant risk of unexpected disabling hypoglycaemia or of hypoglycaemia unawareness should be suspected in adults with type 1 diabetes who have: • lower HbA1c levels, in particular levels in or approaching the normal reference range (DCCT harmonised < 6.1%) • HbA1c levels lower than expected form self-monitoring results.	Delete.	Replaced by: Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review. [recommendation 84] Review insulin regimens and doses and prioritise strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, including: • reinforcing the principles of structured education • offering continuous subcutaneous insulin infusion (CSII or insulin pump) therapy • offering real-time continuous glucose monitoring. [recommendation 90] If impaired awareness of hypoglycaemia is associated with recurrent severe hypoglycaemia despite these interventions, consider referring the person to a specialist centre. [recommendation 91]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
49	Where experience or risk of hypoglycaemia is significant to an individual, or the effort needed to achieve target levels severely curtails other quality of life despite optimal use of current diabetes technologies, tighter blood glucose control should not be pursued without balanced discussion of the advantages and disadvantages.	Delete.	Replaced by: Ensure that adults with type 1 diabetes with impaired awareness of hypoglycaemia have had structured education in flexible insulin therapy using basal–bolus regimens and are following its principles correctly. [recommendation 87] Offer additional education focusing on avoiding and treating hypoglycaemia to adults with type 1 diabetes who continue to have impaired awareness of hypoglycaemia after structured education in flexible insulin therapy. [recommendation 88] Avoid relaxing individualised blood glucose targets as a treatment for adults with type 1 diabetes with impaired awareness of hypoglycaemia. [recommendation 89] Review insulin regimens and doses and prioritise strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, including: • reinforcing the principles of structured education • offering continuous subcutaneous insulin infusion (CSII or insulin pump) therapy • offering real-time continuous glucose monitoring. [recommendation 90]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			If impaired awareness of hypoglycaemia is associated with recurrent severe hypoglycaemia despite these interventions, consider referring the person to a specialist centre. [recommendation 91]
50	Adults with type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being.	Delete.	This recommendation has been removed because it has no clear meaning.
52	Multiple insulin injection regimens, in adults who prefer them, should be used as part of an integrated package of which education, food and skills training should be integral parts.	Delete.	Replaced by: Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. [recommendation 60]
53	Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes.	Delete.	Replaced by: Support adults with type 1 diabetes to make the best use of data from self-monitoring of blood glucose through structured education (see recommendations 12 and 14). [49]
54	Meal-time insulin injections should be provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues before main meals.	Delete.	Replaced by: Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. [recommendation 66]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
55	Rapid-acting insulin analogues should be used as an alternative to meal-time unmodified insulin: • where nocturnal or late inter-prandial hypoglycaemia is a problem • in those whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired.	Delete.	Replaced by: If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin. [recommendation 68]
56	Basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at meal times or the midday insulin dose is small If rapid-acting insulin analogues are given at meal times or the midday insulin dose is small or lacking, the need to give ispohane (NPH) insulin twice daily (or more often) should be considered.	Delete.	Replaced by: Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. [recommendation 62]
57	Long-acting insulin analogues (insulin glargine) should be used when: • nocturnal hypoglycaemia is a problem on isophane (NPH) insulin • morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood • glucose control • rapid-acting insulin analogues are used for meal-time blood glucose control.[	Delete.	Replaced by: Consider, as an alternative basal insulin therapy for adults with type 1 diabetes: • an existing insulin regimen being used by the person that is achieving their agreed targets • once-daily insulin glargine if insulin detemir is not tolerated or if twice-daily basal insulin injection is not acceptable to the person. [recommendation 63]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
58	Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life. • Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance. • Biphasic rapid-acting insulin analogue pre-mixes may give an advantage to those prone to hypoglycaemia at night. • Such twice daily regimens may also help: • those who find adherence to their agreed lunch-time insulin injection difficult • adults with learning difficulties who may require assistance from others.	Delete.	Replaced by: Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal–bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. [recommendation 69]
59	Adults whose nutritional and physical activity patterns vary considerably from day to day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations (see sections 1.9.3.6–8), and consideration of unusual patterns and combinations.	Delete.	This recommendation has been deleted because the content would be covered by structured education programmes.
60	For adults undergoing periods of fasting or sleep following eating (such as during religious feasts and fasts or after night-shift work), a rapid-acting insulin analogue before the meal (provided the meal is not prolonged) should be considered.	Delete.	This recommendation has been deleted because a good basal-bolus regimen, as recommended in recommendation 60, should be able to accommodate a period of fasting and feasting.

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61	For adults with erratic and unpredictable blood glucose control (hyper- and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered: • resuspension of insulin and injection technique • injection sites • self-monitoring skills • knowledge and self-management skills • nature of lifestyle • psychological and psychosocial difficulties • possible organic causes such as gastroparesis.	For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered: • injection technique • injection sites • self-monitoring skills • knowledge and self-management skills • nature of lifestyle • psychological and psychosocial difficulties • possible organic causes such as gastroparesis. **[2004, amended 2015]** (recommendation 71)	Reference to resuspension of insulin is out of date and so has been deleted.
62	Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: • multiple-dose insulin therapy (including, where appropriate, the use of insulin • glargine) has failed; and • those receiving the treatment have the commitment and competence to use the • therapy effectively.	Delete.	Replaced by: For guidance on the use of continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes, see Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151). [recommendation 64]
63	Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some meal-time insulin) should be considered for adults starting insulin therapy, until such time as islet B-cell deficiency progresses further.	Delete.	Replaced by: Do not offer non-basal–bolus insulin regimens for treating adults newly diagnosed with type 1 diabetes. [recommendation 62]

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65	Oral glucose-lowering drugs should generally not be used in the management of adults with type 1 diabetes.	Delete.	Replaced by: Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25kg/m^2 or above wants to improve their blood glucose control while minimising their effective insulin dose. [recommendation 74]
66	Adults with diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen.	Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. **[2004]** (recommendation 78)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
68	Insulin injection should be made into the deep subcutaneous fat. To achieve this, needles of a length appropriate to the individual should be made available.	Delete.	Replaced by: Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. [recommendation 75]
69	Adults with type 1 diabetes should be informed that the abdominal wall is the therapeutic choice for meal-time insulin injections.	Delete.	Replaced by: Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point within sites. [recommendation 77]
70	Adults with type 1 diabetes should be informed that extended-acting suspension insulin, for example isophane (NPH) insulin, may give a longer profile of action when injected into the subcutaneous tissue of the thigh rather than the arm or abdominal wall.	Delete.	This recommendation has been deleted because isophane (NPH) insulin is no longer recommended as first line choice for long-acting insulin.
71	Adults with diabetes should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within	Delete.	Replaced by: Advise adults with type 1 diabetes to rotate insulin injection sites and avoid repeated injections at the same point

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	that area.		within sites. [recommendation 77]
72	Adults with diabetes should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers.	Provide adults with type 1 diabetes with suitable containers for collecting used needles. Arrangements should be available for the suitable disposal of these containers. **[2004]** (recommendation 80)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
73	The injection-site condition should be checked annually and if new problems with blood glucose control occur.	Check injection site condition at least annually and if new problems with blood glucose control occur. **[2004, amended 2015]** (recommendation 81)	The GDG clarified that injection site condition can be checked more frequently than annually if appropriate.
74	Adults with type 1 diabetes should be informed that any available glucose/sucrose-containing fluid is suitable for the management of hypoglycaemic symptoms or signs in people who are able to swallow. Glucose-containing tablets or gels are also suitable for those able to dissolve or disperse these in the mouth and swallow the products.	Explain to adults with type 1 diabetes that a fast-acting form of glucose is needed for the management of hypoglycaemic symptoms or signs in people who are able to swallow. Glucose-containing tablets are also suitable. Glucose-containing gels are useful for anyone who is able to use them. **[2004, amended 2015]** (recommendation 92)	The GDG clarified that a fast-acting form of glucose can be used for managing hypoglycaemia. The text specifying tablets or gels has been deleted. Glucogel is no longer listed in the BNF. The BNF also advises that other suitable forms of glucose can be used and therefore did not want to state that only gels and tablets are appropriate.
75	When a more rapid-acting form of glucose is required, purer glucose containing solutions should be given.	Delete.	This recommendation has been deleted because it is a duplication of recommendation 92.
76	Adults with decreased level of consciousness due to hypoglycaemia who are unable to take oral treatment safely should be: • given intramuscular glucagon by a trained user (intravenous glucose may be used by professionals skilled in obtaining intravenous access) • monitored for response at 10 minutes, and then given intravenous glucose if the level of consciousness is not improving significantly • • then given oral carbohydrate when it is safe to	Adults with type 1 diabetes with a decreased level of consciousness as a result of hypoglycaemia and so are unable to take oral treatment safely should be: • given intramuscular glucagon by a family member or friend who has been shown how to use it (intravenous glucose may be used by healthcare professionals skilled in obtaining intravenous access) • monitored for response at 10 minutes, and then given intravenous glucose if their level of	The GDG clarified that this recommendation relates to people who are unable to protect their airway because of a decreased level of consciousness. Glucagon can be administered in an emergency situation. The Human Medicines Regulations 2012 schedule 19 lists glucagon as a medicine that can be administered in an emergency without a prescription. The MHRA states that 'Regulation 238 of the Human Medicines

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	administer it, and placed under continued observation by a third party who has been warned of the risk of relapse.	consciousness is not improving significantly • then given oral carbohydrate when it is safe to administer it, and placed under continued observation by a third party who has been warned of the risk of relapse. **[2004, amended 2015]** (recommendation 93)	Regulations 2012 allows for certain prescription only medicines to be administered by anyone for the purpose of saving life in an emergency. The medicines this concerns are covered in Schedule 19 and are listed below.' Therefore the recommendation has been changed to reflect that intramuscular glucagon does not have to be given by a trained user. Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
79	Hypoglycaemia unawareness should be assumed to be secondary to undetected periods of hypoglycaemia (< 3.5 mmol/l, often for extended periods, commonly at night) until these are excluded by appropriate monitoring techniques. If present, such periods of hypoglycaemia should be ameliorated.	Delete.	This recommendation has been deleted because it is not really a recommendation and does not give clear advice. The definition of hypoglycaemia unawareness is included in the linking evidence to recommendations table for identification of impaired awareness of hypoglycaemia and the glossary.
80	Specific education on the detection and management of hypoglycaemia in adults with problems of hypoglycaemia awareness should be offered.	Delete	This recommendation has been deleted because it is redundant.
81	Nocturnal hypoglycaemia (symptomatic or detected on monitoring) should be managed by: • reviewing knowledge and self-management skills • reviewing current insulin regimen and evening eating habits and previous physical activity. • choosing an insulin type and regimen with less propensity to induce low glucose levels in the night hours, such as: ○ isophane (NPH) insulin at bedtime ○ rapid-acting analogue with the evening meal	Manage nocturnal hypoglycaemia (symptomatic or detected on monitoring) by: • reviewing knowledge and self-management skills • reviewing current insulin regimen, evening eating habits and previous physical activity. • choosing an insulin type and regimen that is less likely to induce low glucose levels at night. **[2004, amended 2015]** (recommendation 96)	Details about insulin types have been deleted because the information is out of date and inconsistent with other recommendations in this guideline.

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	○ long-acting insulin analogues (insulin glargine) ○ – insulin pump.		
84	Arterial risk factors should be assessed annually, and the assessment should include: • albumin excretion rate • smoking • blood glucose control • blood pressure • full lipid profile (including HDL and LDL cholesterol and triglycerides) • age • family history of arterial disease • abdominal adiposity.	Assess arterial risk factors annually, including: • albuminuria • smoking • blood glucose control • blood pressure • full lipid profile (including HDL and LDL cholesterol and triglycerides) • age • family history of arterial disease • abdominal adiposity. **[2004, amended 2015]** (recommendation 114)	Change made from '[abnormal] albumin excretion rate' to 'albuminuria' for accuracy.
91	Aspirin therapy (75mg daily) should be recommended in adults in the highest and moderately-high-risk categories.	Delete.	Replaced by: Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes. [recommendation 113]
96	Adults who have had myocardial infarction or stroke should be managed intensively, according to relevant non-diabetes guidelines. In the presence of angina or other ischaemic heart disease, beta-adrenergic blockers should be considered. (For use of insulin in these circumstances, see 'Hospital administration and intercurrent disease', Section 1.12.3.)	Provide intensive management for adults who have had myocardial infarction or stroke, according to relevant non-diabetes guidelines. In the presence of angina or other ischaemic heart disease, beta-adrenergic blockers should be considered. (For use of insulin in these circumstances, see section 1.14). For guidance on secondary prevention of myocardial infarction, see the NICE guideline on MI – secondary prevention. **[2004, amended 2015]** (recommendation 119)	Cross-reference to relevant NICE guideline added.
97	Intervention levels for recommending blood pressure management should be 135/85 mmHg unless the	Intervention levels for recommending blood pressure management should be 135/85 mmHg	Change made from '[abnormal] albumin excretion rate' to 'albuminuria' for

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	person with type 1 diabetes has abnormal albumin excretion rate or two or more features of the metabolic syndrome (see section 1.10.1.3), in which case it should be 130/80 mmHg. See also sections 1.11.2.5–7.	unless the adult with type 1 diabetes has albuminuria or 2 or more features of the metabolic syndrome, in which case it should be 130/80 mmHg. See also recommendations recommendation 164–166. **[2004, amended 2015]** (recommendation 120)	accuracy.
99	A trial of a low-dose thiazide diuretic should be started as first-line therapy for raised blood pressure, unless the person with type 1 diabetes is already taking a renin-angiotensin system blocking drug for nephropathy (see 'Nephropathy', Section 1.1 1.2). Multiple drug therapy will often be required.	Start a trial of a renin–angiotensin system blocking drug as first-line therapy for hypertension or nephropathy in adults with type 1 diabetes. **[2004, amended 2015]** (recommendation 122)	The GDG did not review the evidence for this recommendation. However, the NICE guidance on hypertension has changed since CG15 was published in 2004, and thiazides are no longer first-line therapy for any age group. Thiazides can elevate blood glucose. The GDG recommend renin–angiotensin system blockers as first-line therapy. They are recommended in NICE's hypertension guideline as first-line therapy for people under 55 years, which accounts for most adults with type 1 diabetes and hypertension. For people over 55 years who do not have renal impairment, the NICE hypertension guideline recommends calcium channel blockers. As soon as renal impairment or albuminuria is detected, a renin–angiotensin system blocker is recommended for renal protection. Therefore it is sensible to recommend a renin–angiotensin blocker as first-line therapy for all adults with type 1 diabetes if they have hypertension. Mention of nephropathy has been removed; guidance on nephropathy is given in recommendation 164.
100	Adults with diabetes should be offered information on	Provide information to adults with type 1 diabetes	Type 1 diabetes is specified for clarity

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	the potential for lifestyle changes to improve blood pressure control and associated outcomes, and offered assistance in achieving their aims in this area.	on the potential for lifestyle changes to improve blood pressure control and associated outcomes, and offer assistance in achieving their aims in this area. **[2004]** (recommendation 123)	(original wording had 'diabetes' or did not specify diabetes at all).
101	Concerns over potential side effects should not be allowed to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant. In particular: • selective beta-adrenergic blockers should not be avoided in adults on insulin • low-dose thiazides may be combined with beta-blockers • when calcium channel antagonists are prescribed, only long-acting preparations should be used • direct questioning should be used to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes.	Do not allow concerns over potential side effects to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant. In particular: • do not avoid selective beta-adrenergic blockers where indicated in adults on insulin • low-dose thiazides may be combined with beta-blockers • when calcium channel antagonists are prescribed, use only long-acting preparations • use direct questioning to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes. (recommendation 124)	The GDG added 'where indicated' because the indications for beta blockers in pure hypertension are much more reduced now than in 2004. NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, or the verb used has been changed.
102	Eye surveillance for adults newly diagnosed with type 1 diabetes should be started from diagnosis.	Start eye screening for adults newly diagnosed with type 1 diabetes from diagnosis. **[2004]** (recommendation 151)	'eye surveillance' has been changed to 'eye screening', in line with current terminology.
103	Depending on the findings, structured eye surveillance should be followed by: • routine review in 1 year, or • earlier review, or • referral to an ophthalmologist.	Depending on the findings, follow structured eye screening by: • • routine review in 1 year or • • earlier review or • • referral to an ophthalmologist. **[2004]** (recommendation 152)	'eye surveillance' has been changed to 'eye screening', in line with current terminology.
105	The reasons and success of eye surveillance systems should be properly conveyed to adults with type 1 diabetes, so that attendance is not reduced by	Explain the reasons and success of eye screening systems to adults with type 1 diabetes, so that attendance is not reduced by lack of knowledge or	'eye surveillance' has been changed to 'eye screening', in line with current

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	ignorance of need or fear of outcome.	fear of outcome. **[2004]** (recommendation 153)	terminology.
106	Digital retinal photography should be implemented for eye surveillance programmes for adults with type 1 diabetes.	Implement digital retinal photography for eye screening programmes for adults with type 1 diabetes. **[2004]** (recommendation 154)	'eye surveillance' has been changed to 'eye screening', in line with current terminology.
108	Visual acuity testing should be a routine part of eye surveillance programmes.	Make visual acuity testing a routine part of eye screening programmes. **[2004, amended 2015]** (recommendation 156)	'eye surveillance' has been changed to 'eye screening', in line with current terminology. NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
109	Emergency review by an ophthalmologist should occur for: • sudden loss of vision • rubeosis iridis • pre-retinal or vitreous haemorrhage • retinal detachment.	Ensure that emergency review by an ophthalmologist occurs for: • sudden loss of vision • rubeosis iridis • pre-retinal or vitreous haemorrhage • retinal detachment. **[2004, amended 2015]** (recommendation 157)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
110	Rapid review by an ophthalmologist should occur for new vessel formation.	Ensure that rapid review by an ophthalmologist occurs for new vessel formation. **[2004, amended 2015]** (recommendation 158)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.

111	Referral to an ophthalmologist should occur for:
	• referable maculopathy:
	  ○ exudate or retinal thickening within 1 disc
		Refer to an ophthalmologist for:
		• referable maculopathy:
		  ○ exudate or retinal thickening within 1 disc
			The recommendations on eye disease were reviewed by the National Screening Programme and were amended to make them consistent with the current practice

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	diameter of the centre of the fovea ○ circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea) ○ any microaneurysm or haemorrhage within 1 disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse • referable pre-proliferative retinopathy: ○ any venous beading ○ any venous loop or reduplication ○ any intraretinal microvascular abnormalities (IRMA) ○ multiple deep, round or blot haemorrhages (If cotton wool spots are present, look carefully for the above features, but cotton wool spots themselves do not define pre-proliferative retinopathy) • any unexplained drop in visual acuity.	diameter of the centre of the fovea ○ circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea) ○ any microaneurysm or haemorrhage within 1 disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse • referable pre-proliferative retinopathy: ○ any venous beading ○ any venous reduplication ○ any intraretinal microvascular abnormalities (IRMA) ○ multiple deep, round or blot haemorrhages (If cotton wool spots are present, look carefully for the above features, but cotton wool spots themselves do not define pre-proliferative retinopathy) • any large sudden unexplained drop in visual acuity. **[2004, amended 2015]** (recommendation 159)	of the diabetes eye screening programme.
113	If an abnormal surveillance result is obtained (in the absence of proteinuria / urinary tract infection) the test should be repeated at each clinic visit or at least every 3 - 4 months, and the result taken as confirmed if a further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men, > 3.5 mg/mmol for women).	Delete.	For guidance on managing kidney disease in adults with type 1 diabetes see the NICE guideline on chronic kidney disease. [recommendation 160]
115	The significance of a finding of abnormal albumin excretion rate should be discussed with the person	Discuss the significance of a finding of albuminuria with the person concerned. **[2004, amended**	Change made from '[abnormal] albumin excretion rate' to 'albuminuria' for

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	concerned.	**2015]** (recommendation 163)	accuracy.
117	If ACE inhibitors are not tolerated, angiotensin 2 receptor antagonists should be substituted. Combination therapy is not recommended at present.	If ACE inhibitors are not tolerated, substitute angiotensin 2 receptor antagonists. Combination therapy is not recommended. **[2004, amended 2015]** (recommendation 165)	'at present' has been removed in view of evidence known to the GDG that the combination can be harmful, increasing risk of hyperkalaemia and acute renal injury.
129	Men should be asked annually whether erectile dysfunction is an issue.	Delete.	Replaced by: Offer men with type 1 diabetes the opportunity to discuss erectile dysfunction as part of regular review. [recommendation 141]
130	A PDE5 (phosphodiesterase-5) inhibitor drug, if not contraindicated, should be offered where erectile dysfunction is a problem.	Delete.	Replaced by: Offer a phosphodiesterase-5 inhibitor to men with type 1 diabetes with isolated erectile dysfunction unless contraindicated. Choose the phosphodiesterase-5 inhibitor with the lowest acquisition cost. [recommendation 142]
132	In adults with type 1 diabetes on insulin therapy who have erratic blood glucose control or unexplained bloating or vomiting, the diagnosis of gastroparesis should be considered.	Delete.	Replaced by: Consider domperidone[b] (in preference to metoclopramide) for treating gastroparesis[c] in adults with type 1 diabetes. [recommendation 137] Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for

b Although this use is common in UK clinical practice, at the time of consultation (December 2014), domperidone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

c Diagnosis of gastroparesis needing specific therapy can only be made in the absence of hyperglycaemia at the time of testing, because hyperglycaemia induces a physiological delay in gastric emptying.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			adults with type 1 diabetes who have gastroparesis. [recommendation 138] Advise a small-particle-size diet (mashed or pureed food)for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis [recommendation 139] Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations recommendation 137, 138 and 139 are not beneficial or not appropriate. [recommendation 140]
133	In adults with diabetes who have altered perception of hypoglycaemia, the possibility of sympathetic nervous system damage as a contributory factor should be considered.	Delete.	Replaced by: Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review. [recommendation 84] Use the Gold score or Clarke score to quantify awareness of hypoglycaemia in adults with type 1 diabetes, checking that the questionnaire items have been answered correctly. [recommendation 85] Explain to adults with type 1 diabetes that impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia. [recommendation 86]
134	In adults with diabetes who have unexplained	In adults with type 1 diabetes who have	Type 1 diabetes is specified for clarity

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	diarrhoea, particularly at night, the possibility of autonomic neuropathy affecting the gut should be considered.	unexplained diarrhoea, particularly at night, the possibility of autonomic neuropathy affecting the gut should be considered. **[2004]** (recommendation 170)	(original wording had 'diabetes' or did not specify diabetes at all).
136	Adults with diabetes who have bladder emptying problems should be investigated for the possibility of autonomic neuropathy affecting the bladder, unless other explanations are adequate.	In adults with type 1 diabetes who have bladder emptying problems, investigate the possibility of autonomic neuropathy affecting the bladder, unless other explanations are adequate. **[2004]** (recommendation 172)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
137	The management of the symptoms of autonomic neuropathy should include standard interventions for the manifestations encountered (for example, for erectile dysfunction or abnormal sweating).	When managing the symptoms of autonomic neuropathy, include standard interventions for the manifestations encountered (for example, for abnormal sweating and postural hypotension). **[2004, amended 2015]** (recommendation 173)	The GDG added postural hypertension because this is an important manifestation of autonomic neuropathy. There are now separate recommendations about managing erectile dysfunction (recommendation 141–143).
138	For adults with diabetes with diagnosed or suspected gastroparesis, a trial of prokinetic drugs is indicated (metoclopramide or domperidone, with cisapride as third line if necessary).	Delete.	Replaced by: Consider domperidone[d] (in preference to metoclopramide) for treating gastroparesis[e] in adults with type 1 diabetes. [recommendation 137] Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [recommendation 138] Advise a small-particle-size diet (mashed

d Although this use is common in UK clinical practice, at the time of consultation (December 2014), domperidone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

e Diagnosis of gastroparesis needing specific therapy can only be made in the absence of hyperglycaemia at the time of testing, because hyperglycaemia induces a physiological delay in gastric emptying.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
			or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis [recommendation 139] Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations recommendation 137, 138 and 139 are not beneficial or not appropriate. [recommendation 140]
139	Anaesthetists should be aware of the possibility of parasympathetic autonomic neuropathy affecting the heart in adults with diabetes who are listed for procedures under general anaesthetic and who have evidence of somatic neuropathy or other manifestations of autonomic neuropathy.	Anaesthetists should be aware of the possibility of parasympathetic autonomic neuropathy affecting the heart in adults with type 1 diabetes who are listed for procedures under general anaesthetic and who have evidence of somatic neuropathy or other manifestations of autonomic neuropathy. **[2004]** (recommendation 174)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
145	Professionals should be alert to the psychological consequences of chronic painful neuropathy, and offer appropriate management where they are identified.	Delete.	Replaced by: For guidance on treating chronic diabetic neuropathy, see the NICE guideline on neuropathic pain – pharmacological management. [recommendation 175]
147	Where neuropathic symptoms cannot be adequately controlled, it is useful, to help individuals cope , to explain the: • reasons for the problem • likelihood of remission in the medium term • role of improved glucose control.	Delete.	Replaced by: For guidance on treating chronic diabetic neuropathy, see the NICE guideline on neuropathic pain – pharmacological management. [recommendation 175]
149	Elements of an individualised and culturally appropriate plan will include: • sites and timescales of diabetes education including	Elements of an individualised and culturally appropriate plan will include: • sites and timescales of diabetes education,	Additional elements have been included to make this recommendation comprehensive.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	nutritional advice (see 'Approach to education', Section 1.8.1, and 'Dietary management', Section 1.8.3) • initial treatment modalities (see 'Insulin regimens', Section 1.9.3, and 'Insulin delivery', Section 1.9.4) • means of self-monitoring (see 'Self-monitoring of glucose level', Section 1.8.2) • means and frequency of communication with the professional team • follow-up consultations including surveillance at annual review (see individual late complications recommendations) • management of arterial risk factors (see 'Control of arterial risk', Section 1.10). (1.12.1.2)	including nutritional advice (see sections 1.3 and 1.4) • initial treatment modalities, including guidance on insulin injection (see sections 1.7 and 1.8) • means of self-monitoring and targets (see section 1.6) • symptoms, risk and treatment of hypoglycaemia • management of special situations, such as driving • means and frequency of communication with the diabetes professional team • management of arterial risk factors (see section 1.13) • for women of childbearing potential, implications for pregnancy and family planning advice • follow-up consultations, including frequency of review of HbA1c levels and experience of hypoglycaemia, and surveillance at annual review (see section 1.15) **[2004, amended 2015]** (recommendation 177)	
151	Professionals managing DKA should be adequately trained including regular updating, and be familiar with all aspects of its management which are associated with mortality and morbidity. These topics should include: fluid balance acidosis • cerebral oedema • electrolyte imbalance • disturbed interpretation of familiar diagnostic tests (white cell count, body temperature, ECG)	Professionals managing DKA in adults should be adequately trained, including regular updating, and be familiar with all aspects of its management which are associated with mortality and morbidity. These topics should include: • fluid balance • acidosis • cerebral oedema • electrolyte imbalance • disturbed interpretation of familiar diagnostic tests (white cell count, body temperature, ECG)	The population is specified as adults with DKA for clarity.

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	• respiratory distress syndrome • cardiac abnormalities • precipitating causes • infection management including opportunistic infections • gastroparesis • use of high dependency and intensive care units • and the recommendations below. Management of DKA should be in line with local clinical governance.	• respiratory distress syndrome • cardiac abnormalities • precipitating causes • infection management, including opportunistic infections • gastroparesis • use of high dependency and intensive care units • recommendations 100 to 107 in this guideline. Management of DKA in adults should be in line with local clinical governance. **[2004]** (recommendation 102)	
153	Bicarbonate should not generally be used in the management of DKA.	Do not generally use phosphate replacement in the management of DKA in adults. **[2004, amended 2015]** (recommendation 104)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
155	In the management of DKA, once plasma glucose concentration has fallen to 10–15 mmol/litre, glucose-containing fluids should be given (not more than 2 litres in 24 hours) in combination with higher rates of insulin infusion than used in other situations (for example, 6 U/hour monitored for effect).	In the management of DKA in adults, once the plasma glucose concentration has fallen to 10–15 mmol/litre, give glucose-containing fluids (not more than 2 litres in 24 hours) in order to allow continued infusion of insulin at a sufficient rate to clear ketones (for example, 6 units/hour monitored for effect). **[2004, amended 2015]** (recommendation 106)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
157	Phosphate replacement should not generally be used in the management of DKA.	Do not generally use phosphate replacement in the management of DKA in adults. **[2004, amended 2015]** (recommendation 108)	NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
159	To reduce the risk of catastrophic outcomes in DKA,	To reduce the risk of catastrophic outcomes in	The population is specified as adults with

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	monitoring should be continuous and review should cover all aspects of clinical management at frequent intervals.	adults with DKA, ensure that monitoring is continuous and that review covers all aspects of clinical management at frequent intervals. **[2004, amended 2015]** (recommendation 110)	DKA for clarity. NICE has made editorial changes to the original wording to clarify the action to be taken (no change to meaning): a verb has been added, the verb used has been changed or other wording has changed for clarification.
161	Throughout the course of an inpatient admission, the personal expertise of adults with type 1 diabetes (in managing their own diabetes) should be respected and routinely integrated into ward-based blood glucose monitoring and insulin delivery, using the person with type 1 diabetes' own system. This should be incorporated into the nursing care plan.	Throughout the course of an inpatient admission, respect the personal expertise of adults with type 1 diabetes (in managing their own diabetes) and routinely integrate this into ward-based blood glucose monitoring and insulin delivery. **[2004, amended 2015]** (recommendation 133)	The GDG advised removing 'using the person's own systems', because hospitals increasingly use monitoring systems that are quality controlled and recorded automatically into electronic patient records that can be reviewed remotely by the diabetes professional team. The updated recommendation does not preclude the person using their own system in addition to the hospital system if they wish to do so. Use of such hospital monitoring systems improves patient care.
162	Throughout the course of an inpatient admission, the personal knowledge and needs of adults with diabetes regarding their dietary requirements should be a major determinant of the food choices offered to them, except when illness or medical or surgical intervention significantly disturbs those requirements.	Throughout the course of an inpatient admission, the personal knowledge and needs of adults with type 1 diabetes regarding their dietary requirements should be a major determinant of the food choices offered to them, except when illness or medical or surgical intervention significantly disturbs those requirements. **[2004]** (recommendation 134)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
163	Hospitals should ensure the existence and deployment of an approved protocol for inpatient procedures and surgical operations for adults with Type 1 diabetes. This should aim to ensure the maintenance of near-normoglycaemia without risk of	Delete.	Replaced by: Aim for a target plasma glucose level of 5–8 mmol/litre for adults with type 1 diabetes during surgery or acute illness. [recommendation 126]

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	acute decompensation, usually by the use of regular quality-assured blood glucose testing driving the adjustment of intravenous insulin delivery.		Establish a local protocol for controlling blood glucose levels in adults with type 1 diabetes during surgery or acute illness to achieve the target level. [recommendation 127]
165	Optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, should be provided to all adults with diabetes who have threatened or actual stroke. Critical care and emergency departments should have a protocol for such management.	Provide optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, to all adults with type 1 diabetes with threatened or actual myocardial infarction or stroke. Critical care and emergency departments should have a protocol for such management. **[2004, amended 2015]** (recommendation 136)	The GDG confirmed that this recommendation is also important for adults with type 1 diabetes with threatened or actual myocardial infarction. Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
167	Healthcare professionals should be alert to the possibility of the development of other autoimmune disease in adults with type 1 diabetes (including Addison's disease, pernicious anaemia and thyroid disorders).	Be alert to the possibility of the development of other autoimmune disease in adults with type 1 diabetes (including Addison's disease and pernicious anaemia). For advice on monitoring for thyroid disease, see recommendation 147. **[2004, amended 2015]** (recommendation 112)	Mention of thyroid disorders has been deleted because thyroid disease is now covered by a separate recommendation to measure TSH levels at annual review.
168	Members of professional teams providing care or advice to adults with diabetes should be alert to the development or presence of clinical or sub-clinical depression and/or anxiety, in particular where someone reports or appears to be having difficulties with self-management.	Members of diabetes professional teams providing care or advice to adults with type 1 diabetes should be alert to the development or presence of clinical or subclinical depression and/or anxiety, in particular if someone reports or appears to be having difficulties with self-management. **[2004]** (recommendation 179)	Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not specify diabetes at all).
169	Diabetes professionals should ensure that they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds. They should be familiar with appropriate counselling techniques and appropriate drug therapy, while	Diabetes professionals should: • ensure that they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds	Cross-references to relevant NICE guidelines have been added for information. Type 1 diabetes is specified for clarity (original wording had 'diabetes' or did not

Old rec no.	CG15 recommendations	Amended 2015 recommendation (new rec no.)	Reasons for change
	arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with well-being or diabetes self-management.	• be familiar with appropriate counselling techniques and drug therapy, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with wellbeing or diabetes self-management. See also the NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. **[2004, amended 2015]** (recommendation 180)	specify diabetes at all).
170	Special management techniques or treatment for non-severe psychological illness should not be commonly used, except where diabetes-related arterial complications give rise to special precautions over drug therapy.	Delete.	This recommendation has been deleted because it does not give clear advice; leaving it in would cause confusion.
171	Members of multidisciplinary professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with type 1 diabetes with: • over-concern with body shape and weight • low body mass index • poor overall blood glucose control.	Members of diabetes professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with type 1 diabetes with: • over-concern with body shape and weight • low BMI • hypoglycaemia • poor overall blood glucose control. See also the NICE guideline on eating disorders **[2004, amended 2015]** (recommendation 181)	The GDG stated that hypoglycaemia is another possible indicator of eating disorders. Cross-reference to the relevant NICE guideline has been added for information.

Appendix U: NICE technical team

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