Appendix F: Full Health Economics Report

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Any errors and omissions that remain are the responsibility of the NICE Internal Clinical Guidelines team and the GDG.

Contents

1 Introduction

This appendix sets out the original health economic evaluation undertaken to assess the cost effectiveness of pharmacological blood glucose-lowering therapies to control blood glucose levels in people with type 2 diabetes. It was developed by the Internal Clinical Guidelines team at the National Institute for Health and Care Excellence (NICE).

1.1 Decision problem

The health economic analyses address 1 main review question from the guideline scope that is split into 3 sub-questions, based on question prioritisation by the Guideline Development Group (GDG). The main question (question 1) was 'which pharmacological blood glucose-lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?' The 3 sub-questions address different stages of disease progression (see table 1 and figure 1).

Table 1: PICO format for health economic analysis

Sub question	Population	Interventions	Comparison	Outcomes
1a Initial therapy	People failing to manage their type 2 diabetes on diet and exercise alone	Any oral anti-diabetes drug (OAD) administered alone	Any other OAD administered alone	In order to perform cost–utility analyses, quality adjusted life years were used (QALYs)
1b First intensification	People failing to manage their type 2 diabetes on a single OAD	Any 2 OADs in combination or oral anti-diabetes drug with GLP-1 agonist	Any other 2 OADs in combination or oral anti-diabetes drug with GLP-1 agonist	
1c Second intensification	People failing to manage their type 2 diabetes on any 2 OADs in combination or OAD with GLP-1 agonist	Any 3 OADs, 2 OADs with a GLP-1 agonist or insulin with any combination of other drugs	Any other 3 OADs, 2 OADs with a GLP-1 agonist or insulin with any combination of other drugs	

(a) GLP-1 agonist - glucagon-like peptide-1 agonist

There were a large number of treatment options for each of the sub-questions. The sub-questions addressed type 2 diabetes populations at different stages of disease severity; therefore multiple incremental comparisons were undertaken separately for each sub-question. The GDG restricted the consideration of insulin to sub question 1c (second intensification); no clinical evidence was included for third intensification so it was not modelled.

This analysis did not attempt to define when people were deemed to be failing on their existing diabetes treatments, it was assumed that decision had been taken between the clinician and the person and this analysis addresses what is the most cost-effective therapy to be given at that point.

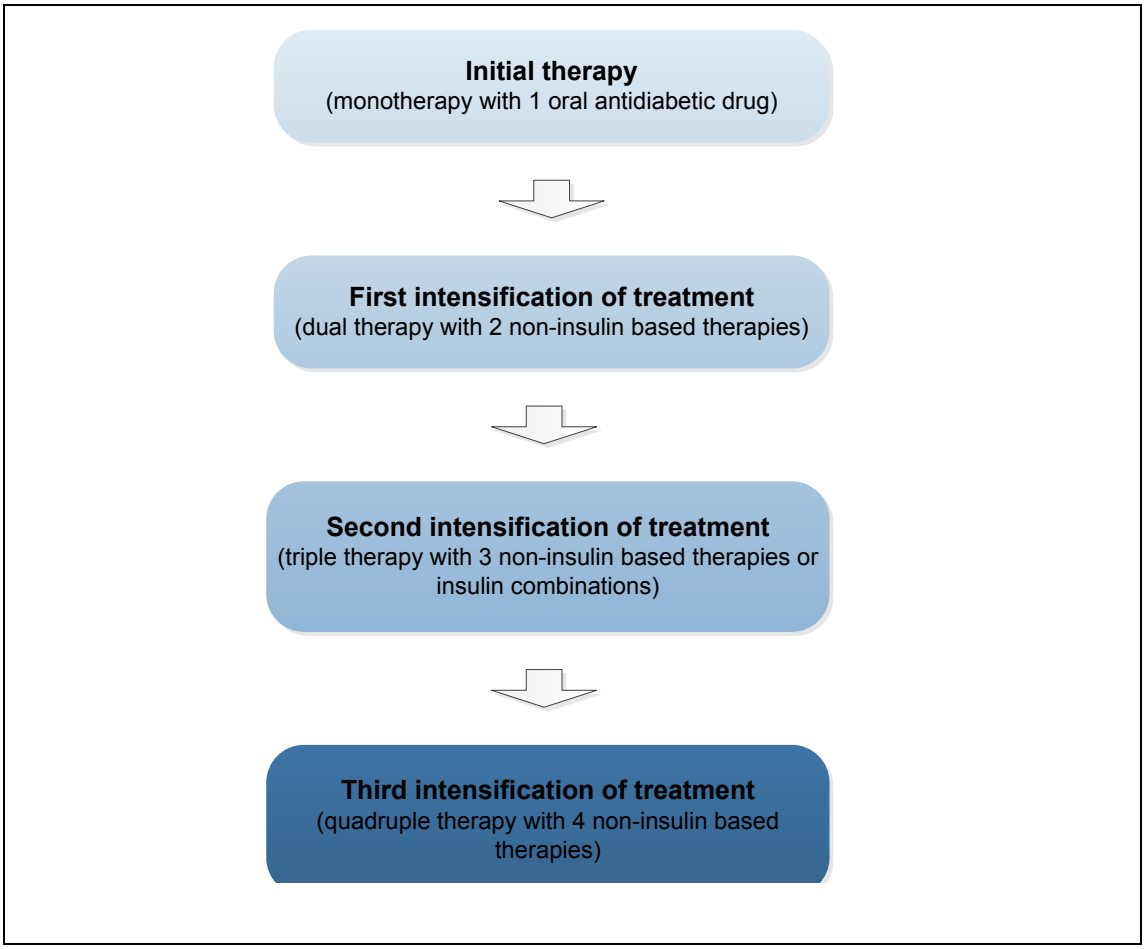


Figure 1: Schematic representation of treatment pathway being modelled

2 Systematic review of existing literature

2.1 Systematic review methods

Previous NICE guidelines on type 2 diabetes (CG66 (National Institute for Health and Care Excellence 2008) and CG87 (National Institute for Health and Care Excellence 2009)) have conducted health economic literature searches focused on specific drug comparisons at second intensification; none have included initial therapy treatment options.

For the current guideline, 1 systematic literature review was undertaken to identify existing cost–utility analyses addressing all 3 sub-questions. No date restrictions were applied and the search was based on the clinical search with a health economic filter applied (searches up to June 2014, see appendix C for the search strategy). The search yielded 3963 unique citations.

2.2 Systematic review results

It is clear that there is an active research field in assessing the cost-effectiveness of pharmacological blood glucose-lowering therapies to control blood glucose levels in people with type 2 diabetes. In total 86 cost–utility analyses (CUAs) that met the NICE reference case (National Institute for Health and Care Excellence 2012b) were found, with around 10 papers published each year (see table 2). Virtually all CUAs compared newer drugs to other comparators, with most CUAs focussed on the United Kingdom (UK), the United States of America (USA) or Canada.

Table 2: Number of type 2 diabetes pharmacological management of blood glucose levels CUAs by publication year

Year	Number of CUAs Published
2003 and earlier	1
2004	2
2005	1
2006	5
2007	9
2008	13
2009	9
2010	8
2011	8
2012	16
2013	7
2014 (searches up to end May)	2

(a) Numbers up to searches at end June 2014. Figures for most recent years may be underestimates as papers may not have been added to electronic databases at time searches were completed

Of the 81 CUAs, 79 were sponsored by a pharmaceutical manufacturer and found the sponsor's drug to be cost-effective. Two health technology appraisal type CUAs found that older, less expensive drugs more cost effective than newer, more costly drugs (Canadian Optimal Medical Prescribing and Utilization Service 2008; Waugh et al. 2010).

To be included in this guideline, in addition to meeting the NICE reference case (National Institute for Health and Care Excellence 2012b) and covering included drug comparisons, 2 further exclusion criteria were agreed by the GDG. Firstly, trial-based CUAs (that is, results not extrapolated to lifetime outcomes) were excluded. Secondly, given the high number of available CUAs the GDG decided to include only UK-based studies.
These criteria resulted in 0 CUAs being included for initial therapies, 2 CUAs for first intensification and 7 CUAs for second intensification. Some of these studies were also included in the previous guideline (National Institute for Health and Care Excellence 2009), but were included again here as the comparisons included were much wider in this guideline. A full list of excluded CUAs along with the exclusion criteria can be found in Appendix F.1 of this document.

2.2.1 Initial therapy

For initial therapy, no CUAs met the UK inclusion criteria and only 2 studies were found worldwide (see Appendix F.1 of this document). It appears no previous published CUA has evaluated the cost effectiveness of single oral anti-diabetes therapies for the pharmacological management of blood glucose in people with type 2 diabetes in the UK.

2.2.2 First intensification

For first intensification, 2 UK CUAs were included (Davies et al. 2012; Schwarz et al. 2008).

Davies et al. (2012) used the Centre for Outcomes Research Diabetes Model (CDM) to compare liraglutide-metformin with both metformin-sulfonylurea (glimepiride) and metformin-sitagliptin for people with type 2 diabetes failing on metformin alone (see table 3 and table 4). Davies et al. (2012) included treatment effects for HbA1c, systolic blood pressure (SBP), cholesterol, weight and hypoglycaemia. People were further intensified onto insulin glargine after 5 years of treatment. The authors found liraglutide-metformin to be cost effective compared with both metformin-sulfonylurea (ICERs £9400/QALY for liraglutide 1.2 mg and £16,500 for liraglutide 1.8 mg) and metformin-sitagliptin (ICERs £9900/QALY for liraglutide 1.2 mg and £10,500/QALY for liraglutide 1.8 mg), but the results were not driven by HbA1c changes and were sensitive to weight progression and utilities.

Whilst Davies et al. (2012) was directly relevant to the UK NHS, it did not cover all the comparisons under consideration for first intensification. The authors gave no details of the weight progression assumptions used (weight-loss could be assumed to have remained for 5 years, or for life), did not use the cheapest insulin within the treatment path and used relatively large utility decrements for weight-gain and hypoglycaemic episodes. Incremental analyses comparing sulfonylurea and different liraglutide doses or comparing sulfonylurea, sitagliptin and liraglutide were not undertaken. The study was funded by the maker of liraglutide.

Schwarz et al. (2012) used the Januvia Diabetes Economic model (JADE) to compare metformin-sitagliptin with metformin-sulfonylurea (glipizide) for people in Scotland with HbA1c greater than 6.5% (see table 5). Schwarz et al. (2012) included treatment effects for HbA1c, SBP, cholesterol, hypoglycaemia and weight. Further intensification of treatment to basal insulin was modelled when HbA1c was greater than 8.0%. The authors found metformin-sitagliptin to be cost effective compared with metformin-sulfonylurea (ICER €11,500/QALY).

However, no sensitivity analyses were reported for these comparisons in the Scottish part of this multi-country CUA, which was based on unpublished randomised controlled trial (RCT) evidence. It did not cover all the comparisons under consideration for first intensification. The modelled baseline population had a relatively long diabetes duration (10 years). Costs included an undiscussed and unusual cost per kilogram weight-change and costs for hypoglycaemic episodes were only applied in the first annual model cycle. Relatively large utility decrements for weight-gain and hypoglycaemic episodes were used. The study was funded by the makers of sitagliptin.

2.2.3 Second intensification

Seven UK CUAs were included for second intensification, covering 4 broad comparisons (Beaudet et al. 2011; McEwan et al. 2007; Pollock et al. 2012; Ray et al. 2007; Valentine et al. 2005; Waugh et al. 2010; Woehl et al. 2008).

Three CUAs (Ray et al. 2007; Waugh et al. 2010; Woehl et al. 2008) all compared twice-daily exenatide with once-daily insulin glargine (see table 6). All were based on the same RCT evidence (Heine et al. 2005) but reported different results, due to differing treatment effect assumptions, drug price assumptions, weight-loss profiles and weight-loss utilities. Beaudet et al. (2011) compared once-weekly exenatide with twice-daily insulin glargine (see table 6).

Ray et al. (2007) used CDM to compare exenatide-metformin-sulfonylurea with insulin glargine-metformin-sulfonylurea, for people with inadequate type 2 diabetes control. Ray et al. (2007) included treatment effects for HbA1c, SBP, cholesterol, hypoglycaemia, weight and nausea. No further treatment intensification was modelled and weight-loss was assumed to remain for life (but the associated utilities were only applied for 2 years). The authors found exenatide-metformin-sulfonylurea to be cost effective compared with insulin glargine-metformin-sulfonylurea (ICER £22,400/QALY), but the results were sensitive to utilities associated with weight-changes and nausea. At a threshold of £20,000 per QALY, exenatide-metformin-sulfonylurea was cost effective compared with insulin glargine-metformin-sulfonylurea in fewer than 40% of cases.

Whilst Ray et al. (2007) modelled insulin titration costs, they did not cover all the comparisons under consideration for second intensification and did not use the most appropriate comparator for this question (the GDG advised metformin-neutral protamine Hagedorn (NPH) insulin-sulfonylurea would be most appropriate comparator as it is cheaper and more widely used). The authors did not model any further treatment intensifications or model treatment withdrawals and applied a 6-month RCT treatment effect at 1 year. They did not include self-monitoring of blood glucose costs, did not know the UK cost of exenatide and did not report the utilities values used. The study was funded by the maker of exenatide.

Waugh et al. (2010) used the United Kingdom Prospective Diabetes Study Outcomes Model version 1 (UKPDS OM1) to compare exenatide-metformin-sulfonylurea with insulin glargine-metformin-sulfonylurea for people with inadequate type 2 diabetes control. Waugh et al. (2010) was the health economic analysis produced to support the previous NICE type 2 diabetes guideline (National Institute for Health and Care Excellence 2009). The authors modelled males and females separately and included treatment effects for HbA1c, weight, hypoglycaemia and nausea. People on exenatide-metformin-sulfonylurea further intensified to insulin glargine-metformin-sulfonylurea when their HbA1c was greater than 7.5%. The authors found exenatide-metformin-sulfonylurea to be cost effective compared with insulin glargine-metformin-

sulfonylurea only if sufficient weight was lost when taking exenatide-metformin-sulfonylurea (ICERs £19,900/QALY for males and £18,400/QALY for females).

Whilst Waugh et al. (2010) was directly applicable to the UK NHS, the authors did not model any further treatment intensifications, applied a 6-month RCT treatment effect at 1 year and did not model treatment withdrawals. Waugh et al. (2010) did not cover all the comparisons under consideration for second intensification and did not use the comparator judged most appropriate by the current GDG.

Woehl et al. (2008) used the Cardiff diabetes model to compare exenatide-metformin-sulfonylurea with insulin glargine-metformin-sulfonylurea for people with inadequate type 2 diabetes control. Woehl et al. (2008) included treatment effects for weight and hypoglycaemia only (not HbA1c) and modelled treatment discontinuations. The authors found insulin glargine-metformin-sulfonylurea dominated (was less costly and gained more QALYs than) exenatide-metformin-sulfonylurea, even with assumptions more favourable to exenatide.

However, Woehl et al. (2008) did not cover all the comparisons under consideration for second intensification and did not use the most appropriate comparator. No further treatment intensification was modelled. The authors modelled no HbA1c difference, assumed weight-loss remained for life and did not apply utility decrements for weight-change or nausea. The study was funded by the makers of insulin glargine.

Beaudet et al. (2011) used CDM to compare once-weekly exenatide in combination with daily metformin-sulfonylurea with insulin glargine-metformin-sulfonylurea for people with inadequate type 2 diabetes control. Beaudet et al. (2011) included treatment effects for HbA1c, SBP, cholesterol, hypoglycaemia and weight. People taking exenatide intensified to insulin glargine after 5 years. The authors found once-weekly exenatide with metformin-sulfonylurea was cost effective compared with insulin glargine-metformin-sulfonylurea (ICER £10,600/QALY) but the results were sensitive to the then-unknown drug cost, weight utilities and time horizon modelled.

Whilst Beaudet et al. (2011) was directly applicable to the UK NHS and modelled insulin titration costs, the authors did not model treatment withdrawals, did not cover all the comparisons under consideration for second intensification and did not use the most appropriate comparator. The authors applied a 6-month treatment effect at 1 year. The study was funded by the makers of once-weekly exenatide.

Two CUAs (McEwan et al. 2007; Waugh et al. 2010) compared NPH insulin with insulin glargine (see table 7).

McEwan et al. (2007) used the Cardiff diabetes model to compare insulin glargine to NPH insulin for type 2 diabetes people switching to insulin glargine. McEwan et al. (2007) modelled a treatment effect for either HbA1c or hypoglycaemia, though not both at once. The authors found insulin glargine to be cost effective compared with NPH insulin (ICERs £10,000/QALY for hypoglycaemia reduction only and £13,900/QALY for HbA1c reduction only), but these results were sensitive to hypoglycaemia utilities, the cost of insulin glargine and cohort mean weight.

However, McEwan et al. (2007) did not cover all the comparisons under consideration for second intensification and no further treatment intensification was modelled. It was not clear what concurrent OADs people were taking and the treatment effect was not taken from peer reviewed publications. The baseline characteristics used appear extreme (unknown diabetes duration, body mass index [BMI] 26 kg/m^2) and the model does not include all relevant health effects on individuals. The study was funded by the maker of insulin glargine.

Waugh et al. (2010) used UKPDS OM1 to compare metformin-NPH insulin-sulfonylurea with insulin glargine-metformin-sulfonylurea for people with type 2 diabetes on metformin-sulfonylurea with inadequate HbA1c control. Waugh et al. (2010) modelled males and females separately and included treatment effects for weight and hypoglycaemia only. The authors found that insulin glargine-metformin-sulfonylurea was not cost effective compared with metformin-NPH insulin-sulfonylurea (ICERs £281,300/QALY for males and £177,900/QALY for females), but the results were sensitive to baseline weight and weight-related utility changes.

Whilst Waugh et al. (2010) was directly applicable to the UK NHS, the authors did not model further treatment intensification and did not cover all the comparisons under consideration for second intensification.

In a very similar analysis, Waugh et al. (2010) used the UKPDS OM1 to compare insulin detemir-metformin-sulfonylurea with metformin-NPH insulin-sulfonylurea for people with type 2 diabetes on metformin-sulfonylurea with inadequate HbA1c control (see table 8). The authors found insulin detemir metformin-sulfonylurea was not cost effective compared with metformin-NPH insulin-sulfonylurea (ICERs £187,700/QALY for males and £102,000/QALY for females), but again the results were sensitive to baseline weight and weight-related utility changes.

Two CUAs (Pollock et al. 2012; Valentine et al. 2005) compared biphasic insulin with insulin glargine (see table 9).

Pollock et al. (2012) used CDM to compare insulin lispro 75/25 and insulin lispro 50/50 with insulin glargine for type 2 diabetes people already taking insulin. Pollock et al. (2012) only modelled treatment effect for HbA1c (the impact of including a hypoglycaemia treatment effect was explored in sensitivity analyses). The authors found both insulin lispro preparations dominated insulin glargine. In an incremental analysis undertaken for this review (but not done in the source paper), insulin lispro 50/50 dominated insulin lispro 75/25 and insulin glargine, but these results were sensitive to the utilities associated with minor hypoglycaemic episodes.

However, Pollock et al. (2012) did not cover all the comparisons under consideration for second intensification and did not use the most appropriate comparator (cheapest and most widely used). No further treatment intensification was modelled and the model did not include all relevant health effects on individuals. The length of time for which the treatment effect was applied was not clear and people were assumed not to be taking any OADs. The primary sources of cost and utility data were not listed and an incremental analysis was not reported. The study was funded by the maker of insulin lispro.

Valentine et al. (2005) used CDM to compare insulin aspart 70/30 with insulin glargine for insulin-naïve people whose type 2 diabetes was not responding adequately to oral anti-diabetes agents. Valentine et al. (2005) modelled treatment effects for HbA1c, weight and insulin dose. People remained on metformin and thiazolidinediones but stopped other OADs. The authors found insulin aspart 70/30 to be cost effective compared with insulin glargine (ICER £7000/QALY), but the results were sensitive to the level of HbA1c change and the time horizon considered.

However, Valentine et al. (2005) did not cover all the comparisons under consideration for second intensification and did not use the most appropriate comparator. The authors did not model further treatment intensification and applied a 6-month treatment effect at 1 year. The baseline characteristics were taken from a non-UK population and appear extreme compared with similar CUAs (baseline HbA1c 9.8%, age 52, duration 9 years). The utilities used were not listed and the

authors did not appear to model hypoglycaemic episodes. The study was funded by the maker of insulin aspart.

2.3 Systematic review discussion and conclusions

A number of UK-based CUAs that cover comparisons included in this decision space exist. However, none exist for initial therapy and none cover all the comparisons under consideration for first or second intensification. Indeed, all the included CUAs presented only pairwise analyses and all the CUAs apart from Waugh et al. (2010) were funded by the makers of 1 of the drugs under consideration.

Key limitations of the included studies included assuming long length of treatment effects and not using the most appropriate comparator. The GDG noted selective use of comparators that were not the cheapest or most used alternatives could appear to increase the cost effectiveness of a chosen treatment option. CUAs were often selective in their choice of health effects modelled e.g. not modelling hypoglycaemic episodes. Few CUAs model treatment withdrawals and costs are often not varied in sensitivity analyses, or only varied by relatively small amounts.

A conclusion of the previous NICE type 2 diabetes guideline (National Institute for Health and Care Excellence 2009) was that CUAs sponsored by pharmaceutical manufacturers found their own drug to be cost effective. This position has not altered. Indeed, if all the 86 worldwide CUAs were to be included in this systematic review, 84 would be sponsored by pharmaceutical manufacturers and found find in favour of the sponsor's drug.

The absence of directly applicable CUAs with only minor limitations covering all the comparators under consideration for each sub-question for this guideline confirmed the GDG's view that an original economic analysis should be undertaken.

Table 3: First intensification – liraglutide-metformin versus metformin-sulfonylurea (glimepiride)

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Davies et al. (2012) People with type 2 diabetes not responding to first line metformin UK **Partially Applicable**[b,c,d,e] **Potentially Serious Limitations**[a,f,g,h,i]	Effects: RCTs. Base case includes treatment effect on HbA1c, SBP, cholesterol, weight and hypoglycaemia. People switch to basal insulin (glargine) after 5 years Costs: UKPDS and other sources. £2008 Utilities: UKPDS and other sources	CDM (lifetime horizon, unspecified) Baseline data: RCT HbA1c 8.3% Age 55.8 Duration 6 years BMI 31.0 kg/m^2 Discounted at 3.5%. Funded by industry	Liraglutide 1.2mg £3003 Liraglutide 1.8mg £4668	Liraglutide 1.2mg 0.32 QALYs Liraglutide 1.8mg 0.28 QALYs	Liraglutide 1.2mg £9449/ QALY Liraglutide 1.8mg £16,501/ QALY	Liraglutide added to metformin monotherapy leads to improvement in QALYs and is a cost-effective option	ICERs (1.2mg) sensitive to weight progression (£13,175/ QALY) and BMI utility (£11,219/ QALY) In incremental analysis, 1.2mg dominates 1.8mg 1.2mg gains driven by SBP, weight and cholesterol not HbA1c In PSA, 88% chance (1.2mg) and 65% chance (1.8mg) of being cost-effective at £20,000/QALY

a Time horizon unspecified
b Unclear whether clinical effects were statistically significant changes
c Base case includes other clinical impacts than HbA1c
d Initial weight progression not detailed (assumed weight-losses remain for life)
e Didn't use cheapest insulin (NPH)
f BMI and hypo utility decrements greater than similar studies
g Does not conduct incremental analysis (of Liraglutide doses, or against comparators) – ideally would need indirect evidence to make appropriate comparison
h Full OSA not undertaken
i Potential conflict of interest

BMI: body mass index
CDM: Centre for Outcomes Research Diabetes Model
HbA1c: glycated haemoglobin
ICER: incremental cost-effectiveness ratio
KG/M^2: kilograms per metre squared
PSA: probabilistic sensitivity analysis
QALY: quality adjusted life year
RCT: randomised controlled trial
SBP: systolic blood pressure
UK: United Kingdom
UKPDS: United Kingdom Prospective Diabetes Study

Table 4: First intensification – liraglutide-metformin versus metformin-sitagliptin

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Davies et al. (2012) People with type 2 diabetes not responding to first line metformin UK **Partially Applicable**[b,c,d,e] **Potentially Serious Limitations**[a,f,g,h,i]	Effects: RCTs. Base case includes treatment effect on HbA1c, SBP, cholesterol, weight and hypoglycaemia. People switch to basal insulin (glargine) after 5 years Costs: UKPDS and other sources. £2008 Utilities: UKPDS and other sources	CDM (lifetime horizon, unspecified) Baseline data: RCT HbA1c 8.4% Age 55.3 Duration 6 years BMI 32.8 kg/m^2 Discounted at 3.5%. Funded by industry	Liraglutide 1.2mg £1842 Liraglutide 1.8mg £3224	Liraglutide 1.2mg 0.19 QALYs Liraglutide 1.8mg 0.31 QALYs	Liraglutide 1.2mg £9851/ QALY Liraglutide 1.8mg £10,465/ QALY	Liraglutide added to metformin monotherapy leads to improvement in QALYs and is a cost-effective option	ICERs (1.2mg) sensitive to weight progression (£13,752/ QALY) and BMI utility (£11,637/ QALY) In incremental analysis, 1.8mg is cost-effective 1.2mg gains driven by HbA1c and weight In PSA, 77% chance (1.2mg) and 85% chance (1.8mg) of being cost-effective at £20,000/QALY

a Time horizon unspecified
b Unclear whether clinical effects were statistically significant changes
c Base case includes greater than HbA1c impact
d Initial weight progression not detailed (assumed weight-losses remain for life)
e Did not use cheapest insulin (NPH)
f BMI and hypo utility decrements used greater than similar studies
g Does not conduct incremental analysis (of liraglutide doses, or against comparators) – ideally would need indirect evidence to make appropriate comparison
h Full OSA not undertaken
i Potential conflict of interest

BMI: body mass index
CDM: Centre for Outcomes Research Diabetes Model
HbA1c: glycated haemoglobin
ICER: incremental cost-effectiveness ratio
KG/M^2: kilograms per metre squared
PSA: probabilistic sensitivity analysis
QALY: quality adjusted life year
RCT: randomised controlled trial
SBP: systolic blood pressure
UK: United Kingdom
UKPDFS: United Kingdom Prospective Diabetes Study

Table 5: First Intensification of Therapy: Metformin-Sitagliptin Versus Metformin-Sulfonylurea (glipizide)

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusion	Uncertainty
			Cost	Effect	ICER		
Schwarz et al. (2008) People with type 2 diabetes with HbA1c > 6.5% on metformin alone Scotland **Partially Applicable**[a,b,e,f,g,h] **Potentially Serious Limitations**[c,d,l,j,k]	Effects: RCT. Base case includes treatment effect on HbA1c, SBP, cholesterol, hypoglycaemia and weight Includes dropouts and treatment intensification (when HbA1c> 8.0%) to basal then basal-bolus insulin Costs: UKPDS. Hypo and BMI costs not sourced. €2007 (assumed) Utilities: UKPDS and other sources	JADE model (lifetime horizon, unspecified) Baseline data: SHS HbA1c 7.52% Age 64.9 Duration 10 years BMI 31.3 kg/m^2 Covers 6 countries and other therapy comparisons Discounted at 3.5%. Funded by industry	€1097	0.095	€11,547/ QALY	Adding sitagliptin to ongoing metformin treatment is cost-effective	No sensitivity analysis for sitagliptin versus sulfonylureas

a Paper based on Scotland, rather than England and Wales
b Time horizon unspecified
c Potentially long duration of diabetes for first intensification of treatment
d RCT data unpublished and analysed per-protocol (not intention-to-treat)
e Base case includes other clinical impacts than HbA1c
f Cost year not explicitly stated
g Includes a cost per kg change in weight (source not given)
h Hypoglycaemia costs applied in first cycle only
i BMI and hypo utility decrements used greater than similar studies
j Full OSA not undertaken
k Potential conflict of interest

BMI: body mass index
HbA1c: glycated haemoglobin
ICER: incremental cost-effectiveness ratio
JADE: Januvia Diabetes Economic Model
KG/M^2: kilograms per metre squared
QALY: quality adjusted life year
RCT: randomised controlled trial
SBP: systolic blood pressure
SHS: Scottish Health Survey
UKPDS: United Kingdom Prospective Diabetes Study

Table 6: Second intensification – exenatide versus insulin glargine

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Ray et al. (2007) People with T2DM on metformin-SU with inadequate control Exenatide (bid) v Glargine (od) UK **Partially Applicable**[a,e,f,h,k] **Potentially Serious Limitations**[b,d,i,j,n,o,q]	Effects: RCT. People remain on treatments for life, weight-loss lasts for lifetime. Also models blood pressure and lipids changes Costs: UKPDS complication costs. Exenatide unknown, priced at USA prices. £2004 Utilities: UKPDS complications, others from Australian and USA sources Utilities for weight-change (lifetime) and nausea applied. Utilities used not shown	CDM (35 year horizon) Baseline data: RCT HbA1c 8.2% Age 59 Duration 10 years BMI 31.3 kg/m^2 Discounted at 3.5%. Funded by industry	£9,912	0.442 QALYs	£22,420/ QALY	Exenatide likely to improve QALYs and represent good value for money compared with glargine. QALY gains attributable to utility changes associated with weight-changes	ICER sensitive to utility changes associated with weight-changes and nausea and discount rates. Model sensitive to immediate rather than long-term QALY differences. In PSA, 80% chance of being cost-effective at £30,000/ QALY. Cost-effectiveness at £20,000/ QALY not quoted in paper, but graph shows <40%
Waugh et al. (2010) People with T2DM on metformin-SU with inadequate control Exenatide (bid) v Glargine (od) UK **Partially Applicable**[j] **Potentially Serious Limitations**[i,k,n,p]	Effects: RCT. Exenatide switch to glargine when HbA1c >7.5%. Models HbA1c, BMI, nausea, hypos. Males and females modelled separately Costs: UKPDS, drug tariff £2007 Utilities: UKPDS, CODE-2, HODaR	UKPDS model (40 year horizon) Baseline data: expert opinion HbA1c: 7.5% Age 58 Duration 5 years BMI 30 kg/m^2 Discounted at 3.5%	Male £1,151 Female £902	Male 0.058 QALYs Female 0.049 QALYs	Male £19,854 /QALY Female £18,408 /QALY	Assuming sufficient weight is lost, exenatide, compared with glargine, appears cost-effective	ICER highly sensitive to BMI related utility and sensitive speed of HbA1c evolution No PSA reported

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Woehl et al. (2008) People with T2DM on metformin-SU with inadequate control Exenatide (bid) v Glargine (od), UK **Partially Applicable**[a,j,l] **Potentially serious limitations**[c,g,h,n,p,q]	Effects: RCT. People remain on treatments for life, weight-loss lasts for lifetime. Models weight-change, hypos, discontinuations only Costs: Drug costs from UK means. Complication costs from UKPDS, inflated by GDP. £2007 Utilities: UKPDS, HODaR for hypos. No disutility for weight-change or nausea	Cardiff model (40 year horizon) Baseline data: RCT and UKPDS HbA1c 7.1% Age 59 Duration unknown BMI 31.9 kg/m^2 Discounted at 3.5%. Funded by industry	£4796	-0.162 QALYs	Glargine dominated exenatide	Insulin glargine dominated exenatide	ICER sensitivity not reported Glargine still dominated in a scenario analysis with longer term HbA1c changes, longer weight-loss differences and higher insulin glargine dosages (with associated more hypoglycaemia) No PSA reported
Beaudet et al. (2011) People with T2DM on Metformin+SU with inadequate control Exenatide (qiw) v Glargine (od), UK **Partially applicable**[a,j] **Potentially serious limitations**[i,k,n,q]	Effects: RCT. Exenatide People switch to glargine after 5 years Costs: UKPDS. Exenatide (qiw) price unknown, priced as other GLP-1 agonists. £2009 Utilities: UKPDS, CODE-2 and other sources	CDM (50 year horizon) Baseline data: RCT and CG87 HbA1c 8.3% Age 58 Duration 8 years, BMI 32.3 kg/m^2 Discounted at 3.5%. Funded by industry.	£1934	0.183 QALYs	£10,597/ QALY	Exenatide once-weekly within range considered cost effective compared with glargine	ICER sensitive to drug cost, BMI utility impact and time horizon If exenatide once-weekly is priced as Liraglutide 1.8mg (1.2mg in base case), ICER is £21,996/QALY In PSA 75% change of being cost-effective at £20,000/QALY threshold

a Nausea included, but other gastrointestinal symptoms not included
b Costs shown do not match claimed source/year
c Costs inflated by Treasury GDP factor rather than HCHS index factor
d Does not include self-monitoring of blood glucose costs
e Utilities used not shown in paper
f Body weight and nausea utilities applied for 2 years only
g No utility applied to weight-changes or nausea
h People remained on exenatide for life (with associated weight-loss) and did not progress to insulin (with associated weight-gain)
i 6 month treatment effect applied at 1 year
j Most appropriate comparator not used
k CUA did not model treatment withdrawals
l No justification given for choosing source of different baseline characteristics
m Baseline characteristics assumed
n Full OSA not reported
o PSA results at £20,000/QALY not reported
p No PSA reported
q Potential conflict of interest

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
BMI: body mass index CODE-2: Cost of Diabetes in Europe study CDM: Centre for Outcomes Research Diabetes Model GDP: gross domestic product GLP-1 agonist: glucagon-like peptide-1 agonist HbA1c: glycated haemoglobin HCHS: Hospital and community health services HODaR: Health Outcomes Data Repository ICER: incremental cost-effectiveness ratio KG/M^2: kilograms per metre squared OSA: one way sensitivity analysis PSA: probabilistic sensitivity analysis QALY: quality adjusted life year RCT: randomised controlled trial SU: sulfonylureas T2DM: type 2 diabetes mellitus USA: United States of America UK: United Kingdom UKPDS: United Kingdom Prospective Diabetes Study							

Table 7: Second intensification – NPH insulin versus insulin glargine

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
McEwan et al. (2007) People with T2DM switching to insulin glargine Glargine v NPH insulin, UK **Partially Applicable**[a,b,c] **Potentially serious limitations**[d,e,f,g]	Effects: Systematic reviews. Either changes in hypoglycaemia or HbA1c modelled. People remain on treatments for life Costs: UKPDS complication costs. Inflated using UK treasury rates. £2005 Utilities: UKPDS and HODaR	Cardiff model (40 year horizon) Baseline data: THIN database HbA1c: 9.0% Age 58 Duration unknown BMI 26.4 kg/m^2 Discounted at 3.5%. Funded by industry	Hypo reduction only: £1,541 HbA1c reduction only: £1,114	Hypo reduction only: 0.111 QALYs HbA1c reduction only: 0.111 QALYs	Hypo reduction only: £10,027/ QALY HbA1c reduction only: £13,921/ QALY	Glargine is cost effective when used to treat people with type 2 diabetes in the UK, compared with NPH insulin	ICER sensitive to price of glargine, hypoglycaemia utilities and cohort mean weight. No PSA reported
Waugh et al. (2010) People with T2DM on metformin-SU with inadequate control Glargine v NPH insulin, UK **Directly Applicable** **Potentially serious limitations**[d,e,f]	Effects: Own meta-analysis, no difference in HbA1c. Reduction in BMI and hypo events. Males and females modelled separately Costs: UKPDS, drug tariff £2007 Utilities: UKPDS, CODE-2, HODaR	UKPDS model (40 year horizon) Baseline data: expert opinion HbA1c: 7.5% Age 58 Duration 5 years BMI 30 kg/m^2 Discounted at 3.5%	Male £1,855 Female £1,780	Male 0.007 QALYs Female 0.010 QALYs	Male £281,349 /QALY Female £177,940 /QALY	NPH should be preferred as first line insulin, rather than a long acting analogue. The analogues have modest advantages but at present much higher costs.	ICER sensitive to baseline BMI and BMI related utility changes No PSA reported

a Length of treatment effect unclear
b Some treatment effect data not published in peer reviewed journals
c Does not include all health effects on individuals
d Baseline characteristics assumed or appear unrealistic
e Full OSA not reported
f No PSA reported
g Potential conflict of interest

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
BMI: body mass index CODE-2: Cost of Diabetes in Europe study HbA1c: glycated haemoglobin HODaR: Health Outcomes Data Repository ICER: incremental cost-effectiveness ratio KG/M^2: kilograms per metre squared NPH: neutral protamine Hagedorn insulin OSA: one way sensitivity analysis PSA: probabilistic sensitivity analysis QALY: quality adjusted life year SU: sulfonylureas T2DM: type 2 diabetes mellitus THIN: The Health Improvement Network database UK: United Kingdom UKPDS: United Kingdom Prospective Diabetes Study							

Table 8: Second intensification – NPH insulin versus insulin detemir

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Waugh et al. (2010) People with T2DM on metformin-SU with inadequate control Insulin detemir v NPH insulin United Kingdom	Effects: Own meta-analysis, Models change in HbA1c, BMI and hypo events. Males and females modelled separately Costs: UKPDS, drug tariff £2007 Utilities: UKPDS, CODE-2, Health Outcomes Data Repository	UKPDS model (40 year horizon) Baseline data: expert opinion HbA1c: 7.5% Age 58 Duration 5 years BMI 30 kg/m^2 Discounted at 3.5%	Male £2,715 Female £unknown	Male 0.015 QALYs Female Unknown QALYs	Male £187,726 /QALY Female £102,007 /QALY	NPH should be preferred as first line insulin, rather than a long acting analogue. The analogues have modest advantages but at present much higher costs.	ICER sensitive to baseline BMI and BMI related utility changes No PSA reported
Directly Applicable							
Potentially serious limitations[a,b,c]							

a 6 month treatment effect applied at 1 year
b Full OSA not reported
c No PSA reported

BMI: body mass index
CODE-2: Cost of Diabetes in Europe study
HbA1c: glycated haemoglobin
ICER: incremental cost-effectiveness ratio
NPH: neutral protamine Hagedorn insulin
OSA: one way sensitivity analysis
PSA: probabilistic sensitivity analysis
QALY: quality adjusted life year
SU: sulonylurea
T2DM: type 2 diabetes mellitus
UKPDS: United Kingdom Prospective Diabetes Study

Table 9: Second intensification – biphasic insulin lispro versus insulin glargine

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Pollock et al. (2012) People with T2DM already on insulin Insulin lispro 75/25 v glargine, lispro 50/50 v glargine, UK **Partially Applicable**[a,c,i] **Potentially Serious Limitations**[e,f,g,h,j,k,l]	Effects: systematic review. Only HbA1c change modelled in base case. People remained on treatments for life Costs: Taken from earlier CUA. Includes concomitant medications but not other OADs. Inflated using CPI. £2008 Utilities: Values not listed, sources not specified	CDM (35 year horizon) Baseline data: UK arm of RCT HbA1c 10.2% Age 59.5 Duration 8 years, BMI 31.9 kg/m^2 Discounted at 3.5%. Funded by industry	Lispro 75/25 v glargine: -£1217 Lispro 50/50 v glargine: -£430	Lispro 75/25 v glargine: 0.09 QALYs Lispro 50/50 v glargine: 0.12 QALYs	Lispro 75/25 dominates glargine Lispro 50/50 dominates glargine:	Lispro 75/25 and 50/50 represent dominant treatment options when compared with long-acting analogue insulins Full incremental analysis shows lispro 50/50 dominates lispro 75/25 and glargine	ICERs sensitive to the inclusion of utilities associated with an increase in minor hypoglycaemic episodes on lispro In PSA, both lispro products have 84% chance of being cost-effective at £30,000/ QALY. Figures for £20,000/ QALY not given or extractable from paper
Valentine et al. (2005) Insulin naïve people withT2DM not adequately responding to OADs Insulin aspart 70/30 v glargine, UK **Partially Applicable**[b,d,i] **Potentially Serious Limitations**[g,j,k,l]	Effects: USA RCT. Modelled changes in HbA1c, BMI and insulin dose. People remained on Metformin and TZDs, but stopped other OADs Costs: UKPDS and other sources. £2004 Utilities: values not listed, sources not specified	CDM (35 year horizon) Baseline data: from USA RCT HbA1c 9.77% Age 52.45 Duration 9 years, BMI 31.45 kg/m^2 Discounted at 3.5%. Funded by industry	£1319	0.19 QALYs	£6951 /QALY	Aspart 70/30 represents value for money compared with glargine	ICER sensitive to HbA1c change and time horizon, but not BMI changes In PSA, 88% chance of being cost-effective at £30,000/QALY. Cost-effectiveness at £20,000/ QALY not quoted in paper, but graph shows >80%

a Length of treatment effect unclear
b 6 month treatment effect applied at 1 year
c Does not include all health effects on individuals
d Baseline characteristics not from relevant population
e Costs inflated by CPI rather than HCHS index factor
f Primary cost sources not listed
g Utility data unclear or utilities used not shown in paper
h Full incremental analysis not undertaken within paper
i Most appropriate comparator not used
j Full OSA not reported
k PSA results at £20,000/QALY not reported
l Potential conflict of interest

Study, Population, Country and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
BMI: body mass index CDM: Centre for Outcomes Research Diabetes Model CPI: Consumer Price Index HbA1c: glycated haemoglobin HCHS: Hospital and community health services ICER: incremental cost-effectiveness ratio KG/M^2: kilograms per metre squared OADs: oral anti-diabetes drugs OSA: one way sensitivity analysis PSA: probabilistic sensitivity analysis QALY: quality adjusted life year RCT: randomised controlled trial T2DM: type 2 diabetes mellitus TZDs: thiazolidinediones USA: United States of America UK: United Kingdom UKPDS: United Kingdom Prospective Diabetes Study							

3 Original health economic model – methods

3.1 Choice of model

As we found no directly applicable CUAs with only minor limitations that covered all the comparators under consideration for each sub-question for this guideline, we undertook an original health economic analysis.

Health economic modelling of diabetes is a rich field. A number of existing models that could be used as the basis for the original analysis were presented to and discussed with the GDG, including an option to construct a completely new model.

The existing models included in the initial GDG discussions were broadly based on those that had competed in the 4th Mount Hood Challenge meeting (Mount Hood 4 Modeling Group 2007; Palmer and The Mount Hood 5 Modeling Group 2013; Yi et al. 2010). At the Mount Hood challenges, diabetes modellers use their models to replicate given RCT outcomes, providing an assessment of the external validity of each model and allowing comparison between models. Results from the 5th Mount Hood Challenge meeting were not available at the time the model was selected (Palmer and The Mount Hood 5 Modeling Group 2013).

The GDG dismissed the option of building a completely new economic model. The group felt that, whilst a new model would give full control over structure and outcomes modelled, the time and expertise required could not be guaranteed to produce a better performing model than the existing models. The group noted that any new model would be highly likely to rely on the same risk equations and data sources as the existing models.

Table 10: Hierarchical model selection

Model	Reference	Reason for Exclusion
Archimedes	Eddy and Schlessinger (2003)	Not available to NICE
Eagle	Mueller et al. (2006)	Not available to NICE
Institute for Medical Informatics and Biostatistics (IMIB) Model	Palmer et al. (2000a) Palmer et al. (2000b)	Not type 2 specific
Diabetes Mellitus Model (DMM)	Brandle et al. (2007)	Not UK specific
Eastman	Eastman et al. (1997a) Eastman et al. (1997b)	Not UK specific
Global Diabetes Model (GDM)	Brown et al. (2000)	Validation not clear
Diabetes Decision Analysis of Cost (DIDACT)	Bagust et al. (2001)	Validation not clear
Januvia Diabetes Economic Model (JADE)	Chen et al. (2008)	Validation not clear
Centre for Outcomes Research Diabetes Model (CDM)	Palmer et al. (2004)	Included for further review
United Kingdom Prospective Diabetes Study Outcomes Model version 1 (UKPDS OM1)	Clarke et al. (2004)	Included for further review

The GDG considered 8 existing models using a set of hierarchical selection criteria (Bagust et al. 2001; Brandle et al. 2007; Brown et al. 2000; Chen et al. 2008; Clarke et al. 2004; Eastman et al. 1997a; Eastman et al. 1997b; Eddy and Schlessinger 2003; Mueller et al. 2006; Palmer et al. 2000a; Palmer et al. 2000b; Palmer et al. 2004). The models had to be:

- Available for NICE to use
- Based on risk equations specific to type 2 diabetes
- Based on UK type 2 diabetes populations and care pathways

- Internally validated (able to reproduce the RCT data on which it was based) and externally validated (able to reproduce results from other RCTs)
- Consistent with the NICE reference case for perspective and outcomes (National Institute for Health and Care Excellence 2012b).

The results of applying these criteria are shown in table 10. The 2 selected models, CDM (Palmer et al. 2004) and UKPDS OM1 (Clarke et al. 2004), are both based on the UKPDS risk equations, costs and quality of life data but CDM also includes other data sources. The GDG viewed these options as showing the best external validation performance in the 4th Mount Hood challenge meeting (Mount Hood 4 Modeling Group 2007; Palmer and The Mount Hood 5 Modeling Group 2013).

Of these 2 options, the GDG expressed a preference for the UKPDS OM1, as it is based on a single large UK type 2 diabetes RCT and directly matches the NICE reference case (National Institute for Health and Care Excellence 2012b). The group was particularly keen to use a model that was based as far as possible on a single RCT. UKPDS OM1 is designed to extrapolate diabetes risk factors to predict long-term outcomes and has been extensively described previously (Clarke et al. 2004; National Institute for Health and Care Excellence 2009). Using UKPDS OM1 was consistent with the previous type 2 diabetes guidelines produced by NICE (National Institute for Health and Care Excellence 2008; National Institute for Health and Care Excellence 2009). We also felt that this option would provide extra modelling flexibility over CDM. CDM allows weight and hypoglycaemia to be modelled, but relies on an external interface that would be difficult to integrate with our own calculations, whereas UKPDS OM1 could be directly programmed for use in our analyses.

The GDG were clear that some of their prioritised short-term outcomes should be modelled, in particular hypoglycaemia and weight-change. This meant original functionality external to UKPDS OM1 would be necessary, similar to what was undertaken in the previous guideline (National Institute for Health and Care Excellence 2009). We noted that the results in the previous guideline (National Institute for Health and Care Excellence 2009) were sensitive to these inputs and the developers were uncertain that their model had adequately converged after 250,000 iterations; clearly, attention would need to be paid to such issues in the current analysis.

The extra modelling flexibility available only via UKPDS OM1 included the ability to model inter-treatment effect correlations. The clinical review comprised multiple treatment option comparisons, evidence for which was combined in single syntheses from which both relative treatment effects and the correlations between treatment effects could be derived. Given the original health economic analysis was required to undertake incremental comparisons, it was necessary to reflect the correlations between treatment effects. These do not appear to have been modelled in any existing CUAs. This is a potentially important consideration from a mathematical standpoint, but it also reflects the clinical reality that a person with type 2 diabetes who experiences a large treatment effect on drug A is also more likely to experience a large treatment effect on drug B. This would not be possible to model for a large number of comparators using CDM.

Similarly, the extra modelling flexibility available via UKPDS OM1 allowed a fully valid probabilistic analysis. The need to integrate uncertainty from UKPDS OM1 parameters and stochastic variation, baseline characteristics, correlated treatment effects and additional hypoglycaemia and weight parameters required a degree of modelling flexibility that was not obviously available in any other model.

However, UKPDS OM1 was not without limitations. These included the age of the underlying RCT, the RCT being based on people with newly diagnosed type 2 diabetes and modelling a limited set of first outcomes only.

The GDG expressed concern about the age of the UKPDS RCT, on which UKPDS OM1 is based. They were concerned that patterns of care may have changed since the UKPDS

RCT. This could affect risk factors (e.g. increased statin use may have altered cholesterol profiles), outcomes (e.g. improvements in stroke care may have altered outcome profiles) and costs (e.g. less care now occurs in hospital). These were noted as limitations, but traded against the size and detail of the UKPDS RCT. It was also noted that no more recent equivalent single source was available and that most diabetes models rely at least in part on the UKPDS RCT. None of the other model options were felt to overcome this limitation.

Similar concerns were expressed regarding applying a model based on people with newly diagnosed type 2 diabetes to later therapy intensifications. However, this limitation may be mitigated by the inclusion of the diabetes duration variable in the UKPDS OM1 equations. Again, none of the other model options presented a solution to this limitation.

The set of outcomes modelled by UKPDS OM1 is limited to the first occurrence of 7 outcomes (Clarke et al. 2004). Other models report outcomes that were not reported in the UKPDS RCT, using data from other RCTs. However, it is hard compare outcomes from different RCTs with confidence, as the RCTs may have employed differing outcome definitions that may lead a model to favour a particular outcome over another. The GDG noted that not all outcomes were modelled by UKPDS OM1, but preferred to have all outcomes from 1 RCT to avoid potential bias.

Van Haalen et al. (2014) recently suggested a stepwise approach with 3 criteria for selecting the right cost-effectiveness model – conceptual validity, model fit and model quality (van Haalen et al. 2014). This article was not available when the model for this guideline was initially selected, but it confirmed an appropriate model was chosen (see table 11).

Table 11: Application of Haalen et al (2014) to selected model

Criteria	Haalen Comments	UKPDS OM1 Comments
Conceptual validity	Is the model an adequate (and pre-specified) representation of the disease and clinical concept?	Could not pre-specify disease and clinical concept, but has been adequately tested in previous CUAs
Model fit	Does the model fit the particular healthcare setting, or can it be easily adapted?	Model based on UK RCT and healthcare system. Parameters such as discount factors, costs and utilities can be easily altered. May need some additional development to capture short term consequences
Model quality	Assess using the Philips et al. checklist	Models assessed using shorter NICE checklist

We initially hoped that an updated version of the UKPDS OM1 would be available during the lifetime of this guideline. Updated risk equations have been published (Hayes et al. 2013). These cover an additional 10 years of follow up (20 years in total), include extra risk factors (high density lipoprotein [HDL], low density lipoprotein [LDL]), BMI, peripheral vascular disease [PVD], atrial fibrillation [AF]) and new outcomes including second events (ulcers, second myocardial infarction [MI], second stroke, second amputation). The UKPDS investigators have also published updated utility values (including utility values for new outcomes (Alva et al. 2014a)), but not updated costs.

The UKPDS investigators plan to publish details of – and make available – an updated health economic model (UKPDS OM2) integrating all these updated analyses. However, this model is not yet available, so we could not use it in developing this guideline. An alternative would have been to use some or all of the new data with the original UKPDS OM1 engine. We decided that this hybrid approach was not sensible, given the absence of some critical parameters (especially costs) and the lack of external validation of the updated risk equations. A wider range of baseline data would also have been needed. Once costs and external validation are available, future CUAs that choose to undertake long-term modelling of interventions for type 2 diabetes should consider using UKPDS OM2.

3.2 Model structure

3.2.1 Model structure – modular approach

The original health economic model to assess the cost-effectiveness of pharmacological blood glucose lower therapies in people with type 2 was based on UKPDS OM1 with additional original functionality (see figure 2).

We adopted a modular approach to constructing and running the model:

- An initial module randomly generated cohorts of people with demographic characteristics, risk factors and event histories that were representative of the appropriate population for the sub-question (see 3.3). The model calculated a year-by-year HbA1c profile for each simulated individual, reflecting the treatment effects estimated for the regimen(s) under simulation (see 3.2.4).
- The model then fed the simulated cohorts (baseline characteristics and HbA1c profiles) through UKPDS OM1, from which results (clinical outcomes, costs and QALYs) were collated. UKPDS OM1 had to be run twice for each cohort:
  - On the first iteration, we set all utility values to 1 and discount rates to 0, in order to produce undiscounted life year outputs.
  - On the second iteration, we reset utilities to the appropriate values (see 3.10.1) and used the required discount rates to produce discounted cost and QALY outputs reflecting the occurrence of long-term macrovascular and microvascular complications of type 2 diabetes.

  As all stochastic processes in UKPDS OM1 can be configured to rely on the same sequences of random numbers, we were able to generate identical cohorts in these 2 iterations.
- The model also generated weight profiles for each simulated individual and estimated incidence of (symptomatic and severe) hypoglycaemic episodes (see 3.2.6 and 3.2.7). It also calculated the incidence and consequences of treatment withdrawal due to adverse events.
- A final results module combined discounted UKPDS OM1 outputs with results from the modelling of weight, hypoglycaemia and adverse events, and also calculated the costs of the drugs under exploration themselves, to give overall results.

We ran the original health economic model separately for each sub-question or therapy level (see figure 1), with different baseline cohorts for each level. Initial therapy and first intensification were modelled using GDG assumptions regarding which therapies would be given at first and second intensification. The GDG based their assumptions on current practice and assumed metformin-sulfonylurea would be the usual choice at first intensification, followed by metformin-NPH insulin at second intensification. Intensification occurred when HbA1c rose above 7.5%.

Because the model relied on treatment effects on HbA1c, weight, hypoglycaemic episodes and treatment dropouts due to intolerance, only treatments for which all 4 data items were available could be modelled (see 3.4). These effects were taken from the clinical review network meta-analyses (NMAs). We did not incorporate treatment effects on other clinical outcomes (such as systolic blood pressure or cholesterol) because the GDG did not prioritise these outcomes for this review question. Moreover, these outcomes were not commonly reported in RCTs; consequently, expanding our minimum dataset to include some or all of them would have substantially reduced the number of comparators that could be modelled (see 3.4).

The original health economic model had annual cycles and was built in Microsoft Excel 2010 (32 bit). A recent version of Microsoft Excel was necessary to give adequate numbers of rows; UKPDS OM1 only interfaced with 32-bit Microsoft Excel. Costs and QALYs were

discounted at 3.5% per annum (National Institute for Health and Care Excellence 2012b). Given the average starting age of people between 60 and 65 (see table 20), we employed a 40-year time horizon.

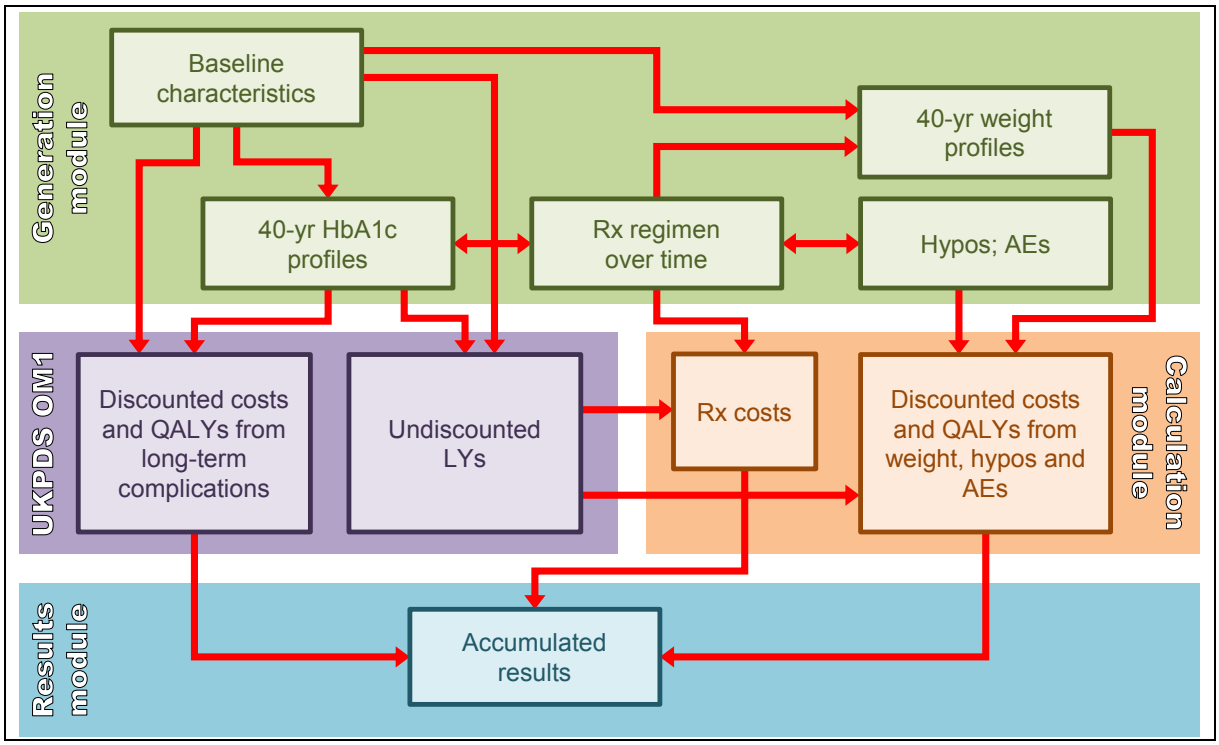


Figure 2: Schematic representation of original health economic model

3.2.2 Modelling of uncertainty

The separation of the original health economic model into separate modules allowed different sources of uncertainty to be kept separate. Recent papers (Davis et al. 14 A.D.; Koerkamp et al. 2011) highlight the need to separately account for and nest the analysis of baseline population heterogeneity, stochastic (first order) uncertainty and parameter (second order) uncertainty. The modules of the original health economic model enabled the various sources of uncertainty to be modelled correctly (see table 12). They also reduced the computer file size which in turn reduced the computer processing time required.

Table 12: Sources of uncertainty within original health economic model

Source of uncertainty	Cohort heterogeneity	Stochastic (first-order) uncertainty	Parameter (second-order) uncertainty
Baseline characteristics	X		X
UKPDS OM1 HbA1c profile	X		X
UKPDS OM1 risk equations	X		X
UKPDS OM1 long-term clinical outcomes	X	X	X
Treatment effects (HbA1c, dropouts, weight, hypoglycaemia)			X
Treatment and other costs, utilities and hypoglycaemia rates			X

There were a number of ways in which uncertainty was propagated within the modules of the original health economic model. Cohort heterogeneity was used to generate cohorts of

people (see 3.3); the same cohort of people was used for each treatment option modelled. Parameter (second order) uncertainty was modelled during PSA iterations (see 3.11.1)

Stochastic (first order) uncertainty within UKPDS OM1 was modelled via what UKPDS OM1 describes as 'loops' – that is, stochastic uncertainty from random sampling against UKPDS outcome equations. Parameter (second order) uncertainty within UKPDS OM1 was modelled via what UKPDS OM1 describes as 'bootstraps' – that is, parameter uncertainty from the use of estimated parameters within UKPDS risk and outcome equations. Parameter (second order) uncertainty also sampled values for all treatment-related efficacy and safety parameters, baseline hypoglycaemia rates, daily drug and consumables costs, UKPDS OM1 long-term outcome costs, severe hypoglycaemia costs, treatment dropout costs and all utility and disutility values.

To ensure UKPDS OM1 parameter uncertainty was appropriately nested with the wider original health economic model parameter uncertainty, we set UKPDS OM1 to rely on a single bootstrapped set of parameters for each probabilistic iteration of the model.

The necessary use of generated cohorts (cohort heterogeneity) and UKPDS OM1 loops (stochastic or first-order uncertainty) meant that it would not be accurate to describe the base-case analyses as deterministic analyses, because some uncertainty was already incorporated into the original health economic model. This is a consequence of random sampling for each person within an individual person modelling environment. Some previous analyses have used single, mean cohort values in their base-case analyses (that is, basing all estimates on the repeated simulation of 1 virtual patient who is configured, so far as is possible, to have the characteristics seen on average the cohort). However, we believe that it is necessary to account for patient-level heterogeneity appropriately: recent research has demonstrated that not doing so may have important consequences for health economic analyses (Vemer et al. 2014).

3.2.3 Model run numbers

The base-case model results presented for each sub-question are the mean of 1000 probabilistic iterations ('outer loops'), for each of which parameters are sampled from appropriate distributions or bootstrapped from the available data (see 3.11.1). Each of these 1000 iterations comprises a unique, randomly generated cohort of 50,000 individuals, each of whom is simulated 100 times ('inner loops') in UKPDS OM1. This means that base-case cost–utility estimates for each treatment option within each sub-question are based on a total of 5 billion model runs.

The large computational requirements of running 1000 PSA iterations were a consideration in selecting the numbers of people and UKPDS loops to run in the base-case analyses. A trade-off was necessary between the numbers of individuals, UKPDS OM1 'inner' loops, bootstraps and 'outer' PSA iterations. There is a complex relationship between these variables: increases in any of them will improve the precision of model outputs though the optimally efficient combination is likely to prioritise parameter ('outer' or PSA) loops over patient ('inner' or UKPDS OM1) loops (O'Hagan et al. 2007). We could not fully access UKPDS parameter uncertainty, which would be necessary to adopt the computationally efficient methods suggested by O'Hagan et al. (2007); however, the combination of patient heterogeneity, 'inner' UKPDS OM1 loops and 'outer' loops should be sufficient to characterise model uncertainty.

We undertook some early model runs to investigate the optimal combination of individuals and 'inner' loops. These analyses were based on the net monetary benefit (at £20,000/ QALY) differences between pioglitazone and sulfonylurea at initial therapy, as our a priori expectation was that the difference between these 2 treatment options would be one of the smallest inter-treatment differences to be modelled. Net monetary benefit (NMB) was used as the outcome to incorporate differences in both costs and QALYs. As figure 3 shows,

10 loops per patient was clearly insufficient to produce stable results, even with large cohorts; however, a good degree of convergence was achieved with cohorts of 35,000 or more patients, and there appeared to be little incremental gain in precision with more than 100 inner loops. Therefore, we concluded that NMB results were adequately converged with 50,000 people per cohort run through 100 UKPDS loops.

Further, for the combination of individuals (50,000) and UKPDS loops (100) chosen, we satisfied ourselves that the remaining Monte Carlo error in both QALYs and costs was sufficiently small (see table 13).

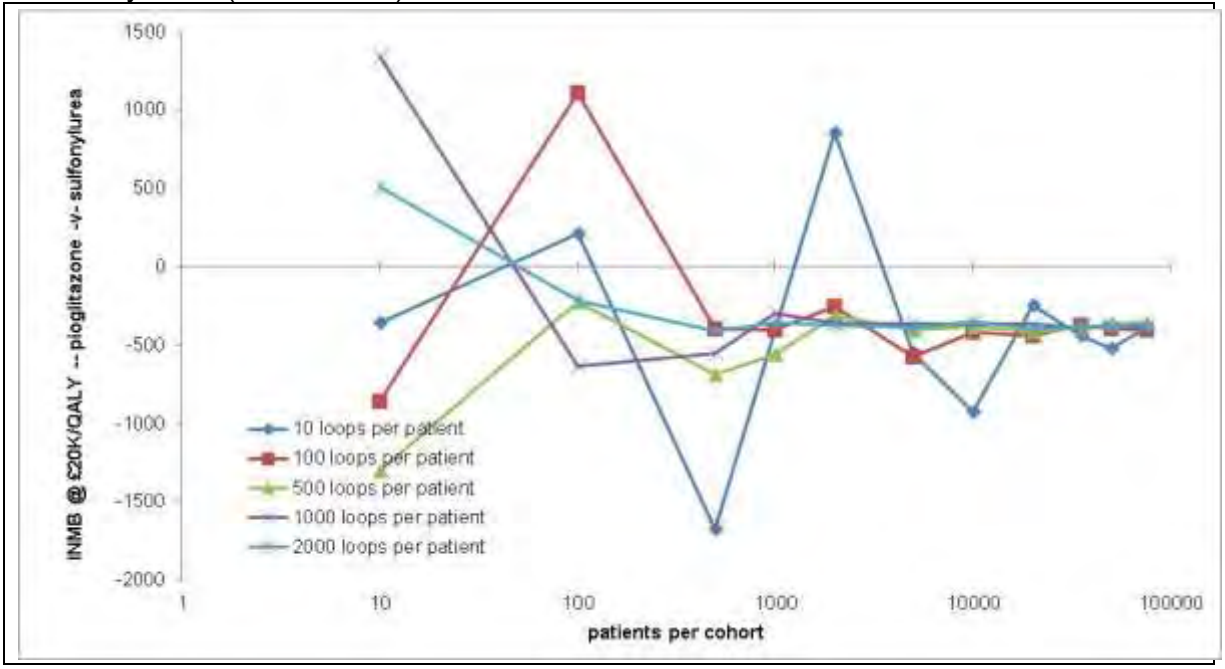


Figure 3: Example of convergence of net monetary benefit values for pioglitazone versus sulfonylurea from initial therapy model

Table 13: Monte carlo error in QALYs and costs with 100 UKPDS loops

Number of simulated individuals in cohort	Monte Carlo error[a] in:	
	QALYs	Costs
10	10.50%	11.91%
100	3.14%	3.87%
500	1.46%	3.14%
1000	1.06%	1.31%
2000	0.74%	1.78%
5000	0.46%	1.68%
10,000	0.33%	0.76%
20,000	0.23%	0.57%
35,000	0.17%	0.42%
50,000	0.14%	0.36%
75,000	0.12%	0.29%

(a) Monte Carlo error is maximum of observations for 4 simulated treatments

3.2.4 HbA1c profiles and treatment effects

HbA1c profiles were generated in the initial module. For initial and first intensification, therapy was intensified when HbA1c rose to greater than 7.5%, to metformin-sulfonylurea then metformin-NPH insulin. Baseline values were generated for each person, treatment

effects were applied from the NMA and, from the second year of each treatment phase onwards, HbA1c profiles followed UKPDS annual risk factor equations (Clarke et al. 2004).

In probabilistic analysis, uncertainty in the UKPDS HbA1c annual risk factor equation parameters was handled by sampling from a multivariate normal distribution (in an identical fashion to the treatment effects; see 3.6). In order to do this, we needed the means and SDs of each coefficient in the equation (these are available in the original publication (Clarke et al. 2004)), and also the correlation matrix representing relationships between the parameters. We derived these correlations from the bootstrapped coefficients from the original UKPDS dataset (see table 14; raw bootstrap data provided by A Gray, personal communication 2013).

Table 14: Correlations between UKPDS HbA1c annual risk factor equation parameters

	Constant	HbA1c (lagged 1 year)	HbA1c at diagnosis	Ln (Year[a])	Year 2[b]
Mean	-0.024	0.759	0.085	0.144	-0.333
SD	0.017	0.004	0.004	0.009	0.050
	Correlation matrix[c]				
Constant	1.000	-	-	-	-
HbA1c (lagged 1 year)	0.251	1.000	-	-	-
HbA1c at diagnosis	-0.217	-0.609	1.000	-	-
Ln (year)	-0.786	-0.293	0.240	1.000	-
Year 2	-0.604	-0.012	0.143	0.412	1.000

(a) Years since diagnosis of type 2 diabetes
(b) Dummy variable equalling 1 when year=2 and 0 otherwise
(c) Bootstraps kindly provided by A Gray (Oxford Universty, personal correspondence 2013)

For all phases of treatment, the value for HbA1c at diagnosis was generated for each simulated individual (see 3.3.3), and represents HbA1c at the point of diagnosis, not at the time of treatment intensification. Similarly, as per the specification of covariates in the UKPDS equations (Clarke et al. 2004), the *year* variable represents time since diagnosis of type 2 diabetes, not time since beginning of the relevant treatment period.

As UKPDS OM1 has annual model cycles, our strong preference was to model treatment effects from the NMA of HbA1c at 1 year (±2 months) only. This is in contrast to a large proportion of published CUAs – whilst all available type 2 diabetes models have annual cycles, many CUAs have used treatment effects from RCTs of less than 1 year duration applied at 1 year (Beaudet et al. 2011; Ray et al. 2007; Valentine et al. 2005; Waugh et al. 2010; Woehl et al. 2008). It is not obvious that clinical effects seen at 6 months will be of the same magnitude at 1 year. The impact of assuming a less than 1-year treatment effect applies at 1 year has not been discussed or tested in the literature. If the relative effects at less than 1 year for 2 or more treatments are taken from the same RCT and applied at 1 year in a model, this may preserve the magnitude of difference. However, type 2 diabetes models use short term changes in HbA1c (and other risk factors) to predict long-term changes in clinical outcomes/events (e.g. MI, stroke) so assuming a greater absolute reduction at 1 year than can be evidenced may impact the cost-effectiveness results.

Only using HbA1c change at 1 year had a number of implications. Firstly, we could not model all the treatments in the clinical decision space. A number of treatments at each therapy level had no included RCTs that reported data at 1 year (see 3.4). Secondly, a substantial amount of clinical data on treatment effects at timepoints less than 1 year could not be included in the HE model. No validated methodology of extrapolating HbA1c data from timepoints less than 1 year to 1 year could be found. Thirdly, although the original health economic model truly represented HbA1c impact at 1 year, the analysis could not differentiate between treatments that may have different rates on HbA1c change within the first year of treatment.

The second intensification analysis was an exception to this rule. Given the weak connections in the NMA for second intensification, the HbA1c data at 1 year were insufficient to form a coherent network. Therefore, any HbA1c data up to 1 year were included in the second intensification NMA – even this assumption only produced a weak network (see section 8.4.12.2 of the main guideline). We acknowledge that this approach is a limitation of the second intensification analysis, but it appears to be no worse than existing CUAs that make similar assumptions about the extrapolation of treatment effects to 1 year. Arguably, the use of a method of synthesis that preserves the randomisation of included trials minimises any bias arising from this approximation.

A small proportion of RCTs reported HbA1c impact at timepoints beyond 1 year. We could potentially have included a 2-year HbA1c impact within the base-case model, as other treatments could have been assumed to follow the UKPDS time paths. However, given the small number of treatments for which these data were available, this was only done as a sensitivity analyses (see 3.11.2.1). This may have biased against treatments with longer-term HbA1c impact.

3.2.5 Treatment dropouts due to intolerance

Existing CUAs have rarely modelled treatment dropouts due to intolerance, particularly for second intensification comparisons. As rates of treatment dropouts due to intolerance were thought to differ between treatments, the GDG felt it was important for the original health economic model to reflect the impact of changing to alternative treatments due to adverse effects.

The GDG felt that, in practice, the number of potential treatment switches due to intolerance at each therapy level would be limited, before switching to a different treatment at that level was dropped in favour of treatment intensification. Two switches (3 treatments in total) were listed (see table 15) and, for modelling simplicity, we assumed no one was intolerant to the third treatment. At second intensification, we only modelled 1 treatment switch due to intolerance.

For initial therapy, the GDG decided people would switch from their existing therapy to metformin, then a sulfonylurea (if they were intolerant of metformin). Where metformin or sulfonylurea were starting therapies, we assumed that a dipeptidyl peptidase-4 (DPP-4) inhibitor would be used for the second switch (vildagliptin was modelled as this was the DPP-4 inhibitor for which the greatest quantity of clinical data was available). The GDG indicated that modified-release metformin would be a switching option after standard metformin. However, we could not include this strategy in the switching rules as modified-release metformin did not meet the minimum dataset (see 3.4).

We applied similar rules at first intensification, following a metformin, sulfonylurea, DPP-4 inhibitor progression. The minimum data were available for a number of DPP-4 inhibitor-metformin treatment options. We chose to model metformin-sitagliptin for treatment switches as that treatment option had more and stronger connections in the NMA.

At second intensification, the GDG indicated people who were intolerant of their first treatment would generally switch to NPH insulin and be likely to continue metformin but discontinue any sulfonylureas. People who were intolerant of NPH insulin would switch to insulin glargine. The potential use of basal-bolus insulin regimens for people who were intolerant of included second intensification treatments was discussed with the GDG, and it was acknowledged that such treatments may be used in practice. However, basal bolus regimens were not within the included RCT NMA and, given the lack of evidence on such regimes, the GDG chose not include them within the switching rules.

Table 15: Treatment switches due to intolerance

Therapy Level	Starting Therapy	First Switch	Second Switch
Initial therapy	Metformin	Sulfonylurea	Vildagliptin
	Sulfonylurea	Metformin	Vildagliptin
	All other treatments	Metformin	Sulfonylurea
First intensification	Metformin-sulfonylurea	Metformin-sitagliptin	Metformin-pioglitazone
	DPP-4 inhibitors-metformin	Metformin-sulfonylurea	Metformin-pioglitazone
	All other treatments	Metformin-sulfonylurea	Metformin-sitagliptin
Second intensification	Any treatment option containing NPH insulin	Insulin glargine-metformin	Not modelled
	All other treatments	Metformin-NPH insulin	Not modelled

(a) Vildagliptin was the chosen DPP-4 inhibitor treatment option at initial therapy as it had the largest RCT evidence base

(b) Metformin-sitagliptin was the chosen DPP-4 inhibitor treatment option at first intensification as it had the largest RCT evidence base

The GDG viewed the treatment switches as applying to people who were randomised to a particular treatment, or who had not experienced other drugs. This allowed them to assume that people were not started on a particular drug because they had shown intolerance to other drugs. For instance, people starting initial therapy on e.g. pioglitazone were randomised to that drug, rather than starting on pioglitazone because they had already shown intolerance to other drugs.

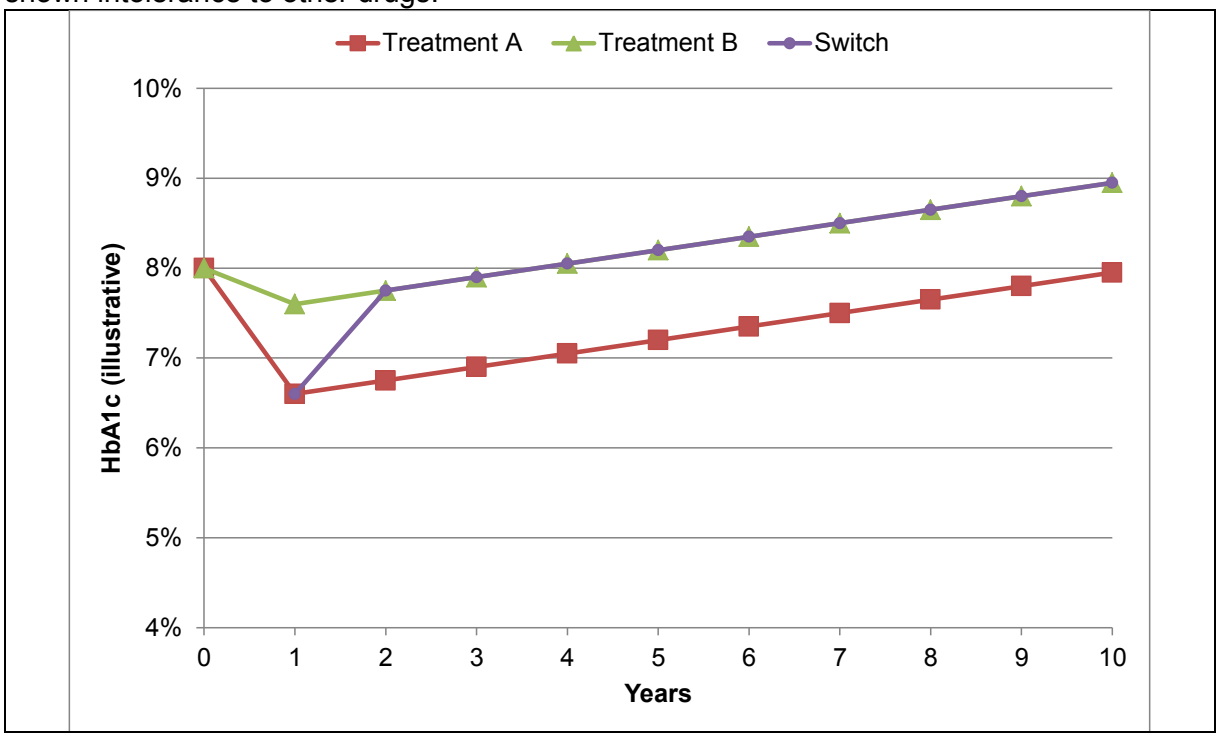


Figure 4: Example of HbA1c profile progression when treatment is switched due to intolerance

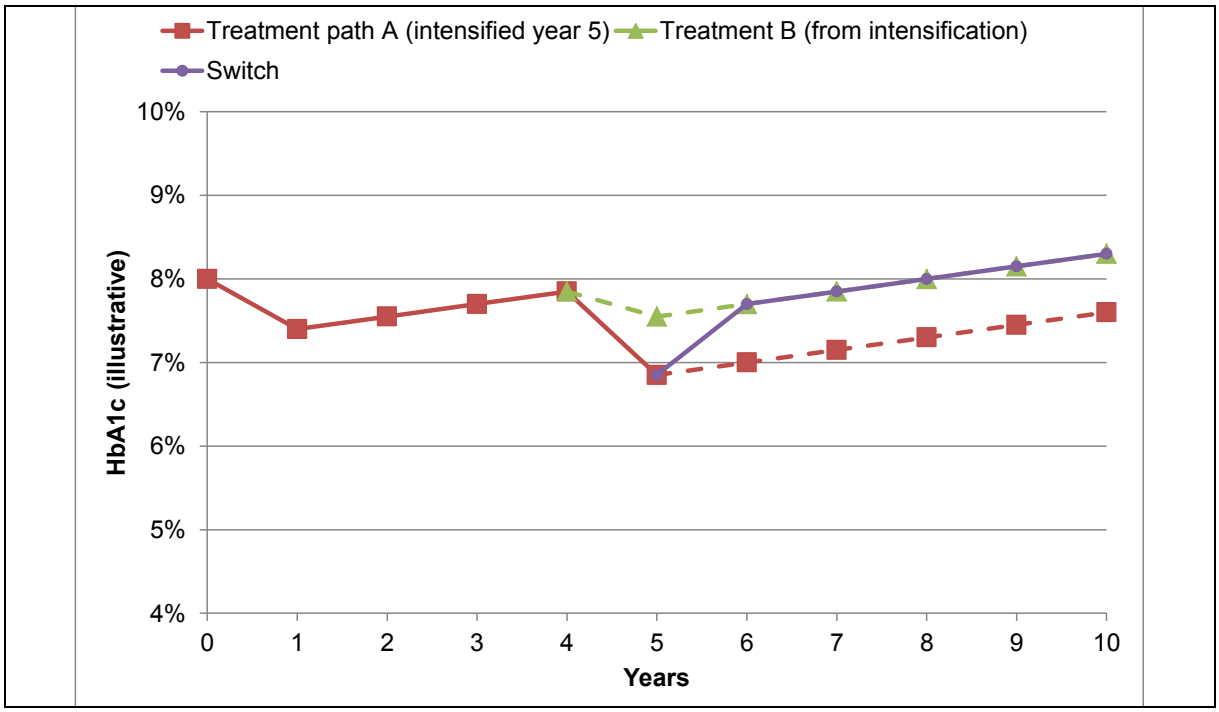


Figure 5: Example of HbA1c profile progression when treatment is switched due to intolerance following previous treatment intensification

When people switched treatments due to intolerance, they received the HbA1c impact from the initial treatment, but the HbA1c effect of the alternative treatment was not applied. This was to avoid incentivising switching to a treatment that may have an additional HbA1c gain. For the new treatment, dropout rates, weight-changes and hypoglycaemia rates were applied. Whilst a person may gain some HbA1c benefit from switching treatments, the GDG felt that they would not gain the same level of benefit as a new person on a treatment and, in the absence of evidence, chose to apply to no HbA1c change.

When a switch occurred at a given timepoint (say, year X) from treatment A to treatment B, a person's HbA1c value switched to what it would have been on treatment B in year X (including natural drift as modelled by the UKPDS risk equation for HbA1c). Figure 4 shows an illustrative example where a switch in therapy occurs at year 3 (baseline values, treatment effects and annual progression all illustrative only).For initial therapy and first intensification, if a person has already intensified treatment and switches a first or second intensification treatment, the switched profile was only applied from the intensification timepoint (see figure 5 - again baseline values, treatment effects and annual progression all illustrative only).

Weight profile at the point of switching was modelled to be equal to baseline weight plus the natural weight a person would have experienced if no treatment had influenced their weight since their initiation in the original health economic model (i.e. 0.1 kg multiplied by the number of years since treatment initiation) plus the impact on weight of the new treatment.

The GDG advised that most treatment intolerances would become apparent within the first few weeks of a treatment being taken. Given an annual cycle length, it was only possible to apply treatment switches at the end of the first year of treatment. This may mean that for those people who were intolerant of a treatment, they made optimistic average gains. For this reason, the model only considered treatment dropouts in the first year of treatment. The GDG also noted that the proposed approach would not explicitly cover any later occurring contraindications, but few if any RCTs were long enough to capture such events. The impact of this limitation is likely to be extremely minor and is a conservative assumption with regards to any potential change in rate over time (assumes that the rate is zero after the first year).

For modelling simplicity, it was necessary to assume that person level treatment intolerances were not carried forward between levels (a 'clean slate' assumption). In particular, treatment switch options at first and second intensification did not account for people who may have been metformin-intolerant, but in the switching rules the GDG felt that clinicians would try to continue metformin treatment wherever possible. Whilst, at a population level, the original health economic model will produce accurate proportions of people intolerant to each treatment, it may be that a simulated person who is randomly deemed to be intolerant of a treatment at initial therapy or first intensification may receive that treatment without being randomly found to be intolerant of a regimen containing that treatment at first or second intensification. This is also noted as a limitation of the analysis; however, we considered it necessary to simplify this aspect of the model in view of data limitations (especially, as noted in 3.4, the absence of evidence on regimens not containing metformin at first intensification).

Switching treatments incurred the cost of additional GP appointment (see 3.9.2) and some utility decrement (see 3.10.2).

3.2.6 Weight profiles

In the UKPDS risk equations (Clarke et al. 2004), weight or BMI was found to be a significant predictor only for congestive heart failure (CHF) events. However, limiting or avoiding of weight-gain has become a key outcome for more recent type 2 diabetes therapies and therefore recent NICE guidelines (National Institute for Health and Care Excellence 2009), NICE technology appraisals (National Institute for Health and Care Excellence 2010; National Institute for Health and Care Excellence 2012a; National Institute for Health and Care Excellence 2013; National Institute for Health and Care Excellence 2014) and published CUAs (see 2.2) have included a utility decrement associated with weight-gain or weight-change.

UKPDS OM1 does not include a facility to include weight-change profiles, so we included these as additional calculations in the original health economic model.

Weight profiles reflected both average natural weight-gain over time (irrespective of treatment) and average treated related weight-change. The GDG agreed to use the average natural weight-gain per year used in the NICE obesity guideline – 0.1 kg per year (National Institute for Health and Care Excellence 2006). The model applied this weight-gain every year irrespective of any treatment-related weight-change that was also applied.

The GDG discussed a number of potential weight profiles for treatment-related weight-change that the health economic model could employ. They considered the following key questions:

- If weight is lost, for how long would the weight-loss be sustained?
- If weight is gained or regained, how much weight is gained or regained and how quickly does that occur?

Table 16: Potential weight change profile assumptions

Assumption	Implication
Weight is lost/gained indefinitely	No evidence to support
Weight lost/gained is reversed over a given period	No evidence as to how long change takes
Weight lost/gained is maintained for duration of evidence only	Weight lost/gained is reversed after 1 model cycle

There were a number of assumptions that could be made with regard to treatment-related weight-change (see table 16). The GDG were clear that all treatments should follow the same profile rules.

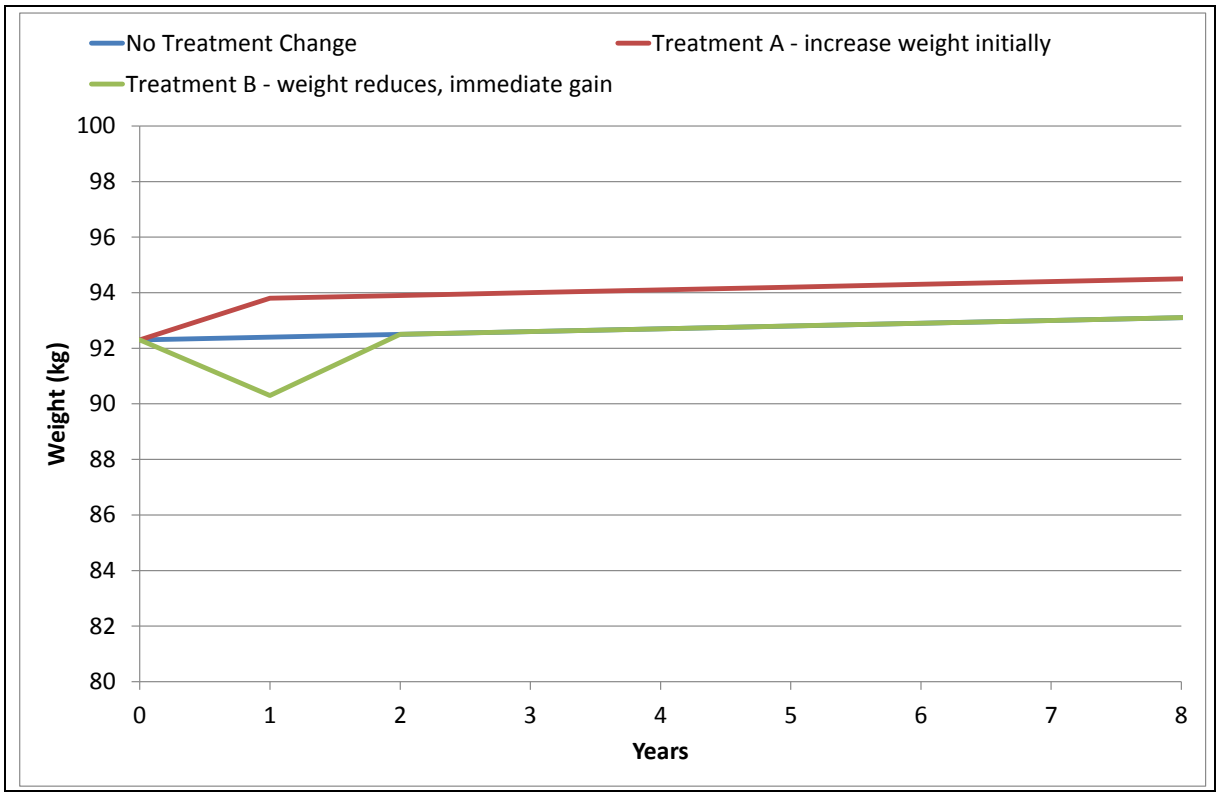


Figure 6: Illustrative weight profile – base-case assumptions

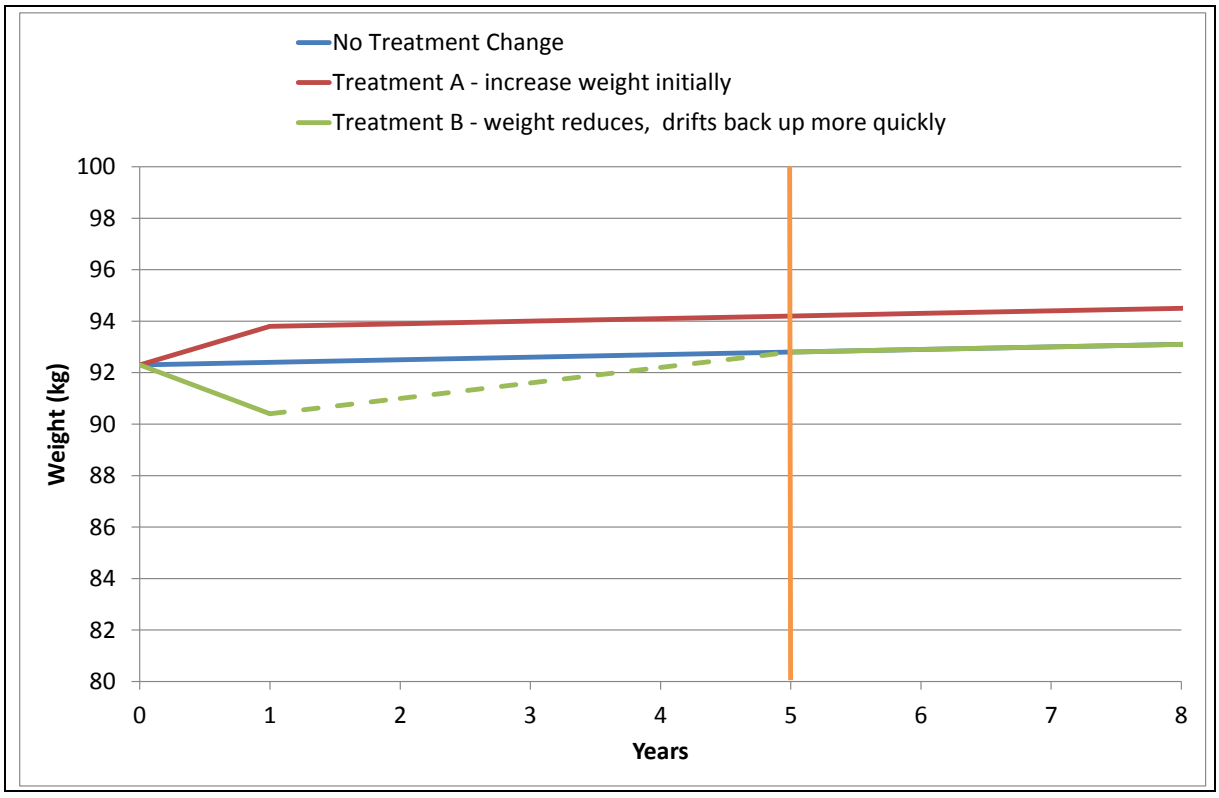


Figure 7: Illustrative weight profile – gradual weight-loss rebound

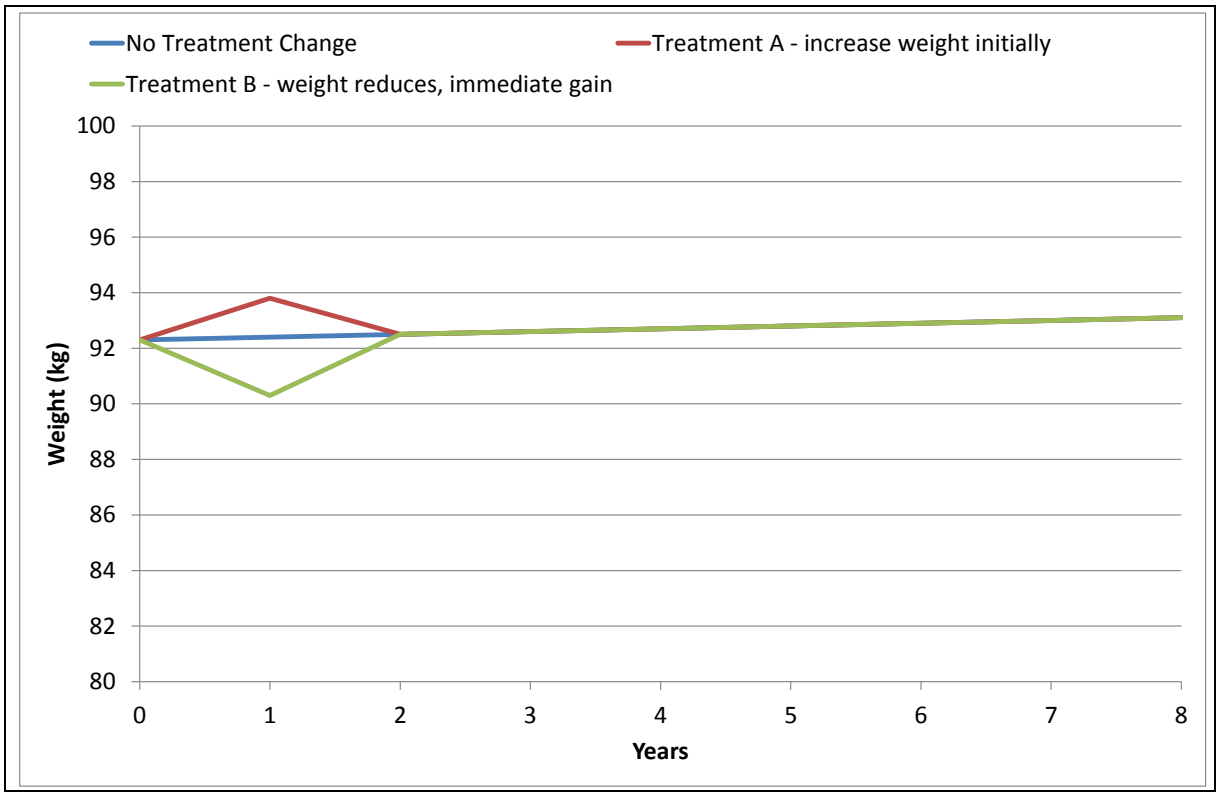


Figure 8: Illustrative weight profile – immediate weight-gain rebound

The simplest assumption possible is that treatment-related weight-change lasts indefinitely. Treatment-related weight-loss could be assumed to be regained after 1 year, in line with the clinical evidence (see figure 6).

Alternatively, treatment-related weight-loss could be assumed to rebound more gradually, over the period the treatment was taken (i.e. up to the next treatment intensification), rather than only lasting 1 year (see figure 7).

Finally, treatment-related weight-gain could be assumed to only last 1 year, in line with the available clinical evidence and the assumption made for weight-loss in the base case (see figure 8).

The GDG felt it was clinically realistic to assume treatment-related weight-gain remained forever, as the GDG agreed that, in their experience, people who gained weight seldom lost it, whereas people often found weight-loss difficult to sustain (see figure 6). The GDG chose to assume that treatment-related weight-loss lasted for only 1 year. This was primarily because the clinical evidence on treatment-related weight-change was presented at 1 year and 2 years, but was very limited at 2 years. Therefore, the GDG chose to apply the treatment effect for weight as per the available evidence. They noted that some people may experience more sustainable weight-loss but the original health economic modelling considered the average person experience.

As for HbA1c, the treatment effect for treatment-related weight-change was taken from the 1-year NMA for initial therapy and first intensification. As before, we concluded that the benefit of using accurate data outweighed the losses from disregarding 3-month and 6-month data. Once more (see 3.2.4), the sparser evidence for second intensification meant it was necessary to base the 1-year treatment effect on data for any period up to 1 year for second intensification.

We believed that it was relatively conservative to assume that treatment-related weight-gain remained indefinitely and treatment-related weight-loss only lasted 1 year; alternative assumptions were tested in sensitivity analyses (see 3.11.2.2).

3.2.7 Hypoglycaemia

Hypoglycaemia rates were not part of UKPDS OM1 and had to be modelled as part of the original health economic model. As hypoglycaemia rates were dependent only on treatment and not on any other risk factor, it was not necessary to feed these data through UKPDS OM1.

The GDG indicated they were most interested in the rates of all hypoglycaemic episodes experienced by people on different treatments, rather than sub categories of hypoglycaemia, such as severe or nocturnal episodes. The GDG felt extra analyses or groupings would not further aid their decision making. However, the group also noted that severe hypoglycaemic episodes were likely to incur costs to the NHS, so these were considered as a subgroup within the original health economic model. The GDG defined severe hypoglycaemic episodes as those where a person required third-party assistance to treat the episode. Episodes that a person could self-treat (i.e. all other non-severe) were defined as symptomatic episodes. The GDG placed a very low priority on nocturnal hypoglycaemic episodes (see table 41) and noted these were included in all hypoglycaemic episodes. Thus nocturnal hypoglycaemic episodes were not analysed separately within the original health economic model.

The original health economic model applied a rate of all hypoglycaemic episodes for each treatment. This is based on a baseline absolute rate for a given treatment in each therapy level, with the relativities from the NMA applied to other treatments. The proportion of all hypoglycaemic episodes that were severe hypoglycaemic episodes (required for resource use and cost purposes; see 3.9.4) was taken from a UK based study (Leese et al. 2003). The GDG felt it was reasonable to assume that the proportion of hypoglycaemia episodes that are severe would be the same across all treatments (2%). We acknowledge that our analysis will be somewhat biased against any treatments that, contrary to this assumption, may have a lower proportion of severe episodes as a proportion of all hypoglycaemic episodes.

Rates of hypoglycaemic episodes were not varied over time. The GDG did not think there was clear evidence for hypoglycaemic episode rates reducing over time (as people with type 2 diabetes adapt to their treatments) or increasing over time (as the disease progresses, dosage of drugs more likely to cause hypoglycaemic episodes increase or control worsens). However, higher and lower rates of hypoglycaemic episodes were tested in sensitivity analyses (see 3.11.2.4).

3.2.8 Nausea

The GDG identified nausea as a key adverse event related to particular treatments and a disutility for treatment-related nausea has been applied in a number of included CUAs (see table 6). However, it was not clear whether applying such a disutility would double-count the adverse event impact, as people with nausea severe enough to impact their utility may have been likely to switch treatments due to intolerance. The GDG advised that the impact of treatment-related nausea was likely to only last 6 weeks; therefore the utility impact may be minimal. Nausea was not modelled as a treatment effect.

3.2.9 Mortality

There is assumed to be no mortality impact beyond that of long-term outcomes and non-diabetes mortality modelled by UKPDS OM1 (Clarke et al. 2004). In particular, the GDG agreed there was no mortality impact of severe hypoglycaemia or from particular treatments. These assumptions are in line with previously published CUAs.

3.3 Baseline data

There is a required baseline dataset for UKPDS OM1, comprising demographics, clinical risk factors at both time of diagnosis and current time and pre-existing complications (see table 20 for list of variables; see Clarke et al. (2004) for full definitions).These can be modelled as population average values, or a dataset of people with different values can be entered. Longitudinal progression of risk factor data can either be supplied as annual datapoints, or as baseline data that are extrapolated using the risk factor time paths in UKPDS OM1 (Clarke et al. 2004). The original health economic model generated a dataset of people and generated annual values for HbA1c only (using the treatment effect data and risk factor time paths).

There were 2 related reasons for generating a dataset of people – reflecting baseline population heterogeneity and modelling correlations between variables. Beyond occasional, limited sensitivity analysis, the importance of the accuracy of the baseline data to the population in question has not been explored in the literature. Similarly, it does not appear that any consideration has been given to the potential impact of correlations between baseline variables. It seems reasonable to consider that, for example, duration of diabetes could be correlated with other variables such as HbA1c. It is not possible to know whether intra-person baseline characteristic correlations influence health economic outcomes without testing such a hypothesis.

Existing analyses often do not appear to differentiate between current risk factors and risk factors at diagnosis – it is not apparent that the previous NICE guideline used different values for each timepoint (National Institute for Health and Care Excellence 2009). Given the progressive nature of type 2 diabetes it would seem necessary, particularly for the first and second intensification questions, to differentiate between diagnosis and current risk factors. The previous NICE guideline (National Institute for Health and Care Excellence 2009) assumed no pre-existing complications in their base-case analysis but noted this was unlikely to be true. Therefore, we included pre-existing complications in our original model.

3.3.1 Baseline data sources considered

In terms of sources of baseline data to populate their models, previous analyses have tended to use either data from expert assumptions (National Institute for Health and Care Excellence 2008; National Institute for Health and Care Excellence 2009), RCT data (usually but not always the RCT from the intervention effect was taken (Davies et al. 2012; Pollock et al. 2012; Ray et al. 2007; Valentine et al. 2005), limited analyses of clinical databases (McEwan et al. 2007) or survey data (Schwarz et al. 2008).

The GDG were keen to source baseline data that accurately reflected potential differences between the populations for the 3 sub-questions. They prioritised sample size, population representativeness and knowledge of therapy level as key drivers in the choice of baseline data-source. The GDG were also keen to use data from clinical practice rather than from RCTs as they were concerned RCT populations may not be reflective of clinical reality when intensifying treatment.

The desire to be able to model correlations between baseline characteristics required either published correlation data, or access to person-level data in order to generate correlation data. This, and the desire for a large sample size and data from clinical practice, led to the consideration of the use of databases of GP records. A number of such databases with similar properties are commercially available, often based on different GP IT systems (e.g. QResearch, Clinical Practice Research Datalink [CPRD], The Health Improvement Network [THIN]).

Table 17: Brief description of potential baseline data sources

Data Source	Details	Missing data	Issues
Health Survey for England (HSE)	Annual random cross sectional sample of 8,600 adults, responses weighted to be nationally representative Approximately 400 people with type 2 diabetes each year (less respondents for clinical variables) 2011 latest available data Clinical measured clinical values Available to researchers via UK data archive portal	Risk factor values at diagnosis No data on atrial fibrillation (AF) or peripheral vascular disease (PVD) Previous existing complications (only stroke and ischaemic heart disease (IHD))	Cannot select data by therapy level Clinical data not available for all people Stroke and IHD data only available from 2011 survey
National Diabetes Audit (NDA)	Annual participatory cross sectional audit of people with diabetes Approximately 2.4 million people with types 2 diabetes in latest report 2013 latest available data Clinical measured clinical values Available to researchers via HSCIC	No correlation data Risk factor data for HDL, PVD, AF, blindness not available	Can only select data by diabetes duration therapy not medication Complication definitions cannot be altered
The Health Improvement Network (THIN)	Regularly updated database of 3.7 million people from 427 UK GP practices on 1 IT system Approximately 131,000 people with type 2 diabetes Last updated 31 August 2013 England and Wales Retrospective Available to NICE via contract with HSCIC	None	Can only select data by diabetes duration therapy not medication Ethnicity data not reliable at individual level

Via the Health and Social Care Information Centre (HSCIC) NICE has an existing contract to access THIN data (The Health Improvement Network (THIN) 2014). National Diabetes Audit (NDA) data (Health and Social Care Information Centre (HSCIC) 2014a) and Health Survey for England (HSE) data (Health and Social Care Information Centre (HSCIC) 2012) were also identified as potential data sources that met all or most of the GDG data requirements. All 3 are large data-sources and are outlined in table 17. It is noted that other GP based databases were available and THIN was only chosen as it was readily available via an existing contract.

None of the 3 potential data-sources perfectly matched UKPDS OM1 and GDG requirements. HSE was substantially smaller than other options and had most missing variables. NDA complications were pre-defined and its definitions did not always match those in UKPDS OM1. THIN does not accurately record ethnicity for individuals. None of the data sources could easily and reliably select data by therapy level.

Of the available options, THIN provided the most comprehensive and accurate risk factor and complication data. It could also provide data at both diabetes diagnosis and current timepoints, but like the other data sources was not easily able to provide data by therapy level. Whilst it was observational rather than randomly selected (like HSE), THIN most accurately covered the complications of interest. Ethnicity is not well recorded at an individual level within THIN.

The GDG felt THIN data provided the best available match to their baseline data requirements.

3.3.2 THIN data selection

People with type 2 diabetes were selected from the THIN dataset using the Read codes in appendix F.2 of this document.

The cohort from whom baseline characteristics were drawn was selected using slightly different methods for the 3 therapy levels.

Initial therapy baseline data were selected from people receiving their first single non-insulin anti-diabetes medication. This was preferred to selecting people at time of diagnosis or a given disease duration, as current recommendations suggest diet and lifestyle advice should be used to manage type 2 diabetes before anti-diabetes medications are prescribed. Data were selected for the point at which people were first prescribed anti-diabetes mediation other than insulin (British National Formulary section 6.1.2 (Joint Formulary Committee 2014)) with measurements recorded closest to the prescription date (± 6 months) were selected.

Given the plethora of drug choices and treatment options available, it was not feasible to select first and second intensification populations on the basis of their recorded medications. The unweighted median reported diabetes duration in the included RCTs were used to derive an estimate of average diabetes duration for each intensification. Median values were used rather than mean values as the distribution of diabetes durations was assumed to be non-symmetrical. This analysis indicated that duration of diabetes was around 4.5 years for people in first intensification papers and 8.5 years in second intensification papers (see table 18). The GDG agreed these diabetes durations appeared reasonable. Therefore, for first and second intensification, measurements closest to the timepoint within selection periods were used.

Table 18: Duration of diabetes from included RCTs

Therapy level	Minimum	Median	Maximum	Selection period
First intensification	1.6 years	4.4 years	9.4 years	2.6-6.5 years
Second intensification	3.3 years	8.6 years	12.5 years	6.5-10.5 years

The GDG discussed using first insulin medication as the selection criteria for second intensification, similar to the way first non-insulin medication was used for initial therapy. However, the decision space for second intensification contained a number of non-insulin-based treatment options and the GDG felt that using first insulin therapy could potentially produce a cohort with worse baseline characteristics than required, particularly for HbA1c as they felt the decision to initiate insulin therapy was often delayed in practice.

The decision points under consideration were what medication to use when a decision to intensify treatment has already been made. The decision is not dependent on a person's existing specific therapy. Therefore, the baseline characteristics did not need to differentiate between people on different existing therapies.

Pre-existing complications were defined in UKPDS OM1 using International Classification of Disease version 9 codes (Clarke et al. 2004), which were converted to Read codes used in the THIN dataset (see appendix F.2 for the Read codes used to extract complication data). To reflect definitions used in the UKPDS analyses, selected complications were first occurrences after diagnosis date but before the timepoint given. Whilst people could have complications that occurred before diagnosis, the UKPDS OM does not require the specification of complications at time of diagnosis.

To ensure data quality, a number of adjustments and exclusions were applied to the THIN dataset.

We did not make any adjustments for missing data. If a risk factor was not recorded the person was excluded from the calculations for that variable. It is not clear whether people

with high or low risk factors are more likely to have missing data so the influence and extent of any bias introduced cannot be assessed. However, we hope that the size of the dataset minimised the impact of any bias.

Risk factor data were cleansed of potential recording errors by excluding the top and bottom 1% of measurements. The resulting minimum and maximum values in the dataset are given in table 19.

Table 19: THIN data set: cleansed data limits

Risk Factor	Minimum Value	Maximum Value
Weight (kg)	50.40	150.00
Height (metres)	1.45	1.90
Cholesterol (mmol/l)	2.59	8.30
HDL (mmol/l)	0.60	2.32
Systolic blood pressure (mmHg)	100.00	188.00
HbA1c (%)	5.10	13.86

(a) Smoking was a categorical variable, so no data cleansing required

People for whom no smoking status was recorded are excluded from the percentage category calculations – this affected up to 20% of the total cohort.

People whose first prescription of anti-diabetes medication (oral or insulin) was before their diagnosis date were excluded – this affected around 10% of the total cohort.

The THIN database does not record the unit of measurement for HbA1c. With the change in standard measurement from percentage to mmol/mol (see section 3.2.1 in the main guideline document) and no date limit applied to the data extracted, the HbA1c field contained a mixture of measurements. To comply with UKPDS OM requirements and outputs from the NMA, data in mmol/mol were converted to percentage using the following formula:

HbA1c % = [HbA1c mmol/mol divided by 10.929] + 2.15

This conversion was carried out prior to the subsequent data validation. In agreement with the GDG, a measurement of less than 20 was assumed to be a percentage rather than mmol/mol.

The UKPDS RCT definition for blindness was “a visual acuity Snellen 6/60 or ETDRS logMAR 1.0 or worse for any reason, persisting for 3 months (ICD-9 codes >=369 and <=369.9)”. It was not possible in THIN to implement the 3 month criteria, so the data may contain people with blindness for a shorter period.

Ethnicity is not well recorded in the THIN dataset. As ethnicity correlation data were available in it, ethnicity data were taken from HSE data. Weighted data for people with doctor diagnosed type 2 diabetes from survey years 2009, 2010 and 2011 were included (1291 people). For variables that were available, raw data were logged to provide the means, standard deviations and correlations natural of logarithm HSE data.

For comparison with the main THIN dataset, basic summary data from this dataset are included in table 22. It was not possible to differentiate between risk factors at diabetes diagnosis and current values; therefore the same ethnicity correlations were used for both risk factor timepoints. Like for the THIN dataset, not all variables were recorded for all people.

It was not possible to select HSE data by therapy level; therefore the same ethnicity data and correlations were used for each level. Whilst individuals are unlikely to alter their ethnicity over time, the total population under analysis changes at each therapy level (as less people

have reached second intensification) so the population-level ethnicity may alter slightly. Any such minor variation could not be modelled.

Weighted correlations are shown in table 23. Note that, to ensure the correlation matrices remained positive-definite, only some of the HSE correlations could be employed. Missing were diagnosis age, age at event, weight. Complications data and at diagnosis data were not available in HSE and therefore correlations not available in HSE data

The GDG noted the limitations of the HSE data. However, this was the only available source of ethnicity data with at least some correlation data available and it was felt that with regard to ethnicity using these data were better than not using any correlation data.

3.3.3 Baseline data values

Baseline THIN data by therapy level data are shown in table 20. Data were presented to the GDG who agreed they appeared clinically realistic and logical across therapy levels. Complication data compared well to that which would be expected for the populations using the UKPDS risk equations, with the exception of MI and IHD. The GDG thought this could be due to changing risk factors, diagnoses and/or patterns of care impacting the occurrence of these complications.

No conclusions should be drawn across timepoints as the cohort changes due to both mortality and the healthy survivor impact of people managing their type 2 diabetes and not reaching the later therapy intensifications.

To allow baseline population heterogeneity to be accurately modelled through UKPDS OM1, individual person data were randomly sampled from a multivariate normal distribution, taking account of correlations between variables. On inspection of the THIN dataset, it was apparent that most continuous risk factor data had positively skewed distributions. Therefore, with the exception of height, continuous risk factor data were modelled as lognormal variables (see table 21). Note that the means, standard deviations and correlations of person-level logged data were used, not the logs of the means and so on. However for clarity, untransformed data are presented here.

It was felt appropriate to apply a minimum to the values of baseline HbA1c which could be generated by the original health economic model. The GDG felt it would be unrealistic to generate a person with a baseline HbA1c of under 6%, as they would not expect to see or treat a person with type 2 diabetes with a HbA1c lower than 6%. The appropriateness of a 6% HbA1c minimum value was confirmed by the minimum value in the cleansed THIN data of 5.1% (see table 19). The 6% minimum value was applied by restricting the sampling from the multivariate normal distribution.

Correlations between baseline variables are shown in table 24, table 25 and table 26. To ensure the correlation matrix remained positive-definite, correlation data are based on the subset of people for whom all variables were recorded.

Despite some limitations, we believe that the use of real-life THIN data with separate data for each intensification represents a real step forward from previous analyses in the quality of baseline data. A large dataset providing separate risk factor data for diabetes diagnosis and current timepoints was used, logged data were used where appropriate and correlations between variables were reflected when baseline population cohorts were generated. In each of these respects, our analysis improves on previous diabetes models.

Table 20: Baseline THIN data used to populate the original health economic model

Category	Characteristic	Number of people			Value		
		Initial Therapy	First Intensification	Second Intensification	Initial Therapy	First Intensification	Second Intensification
Demographics	Number of people	90,219	74,144	43,075	90,219	74,144	43,075
	Ethnicity – White	1291	1291	1291	94.6%	94.6%	94.6%
	Ethnicity – Afro-Caribbean	1291	1291	1291	2.7%	2.7%	2.7%
	Ethnicity – Asian-Indian	1291	1291	1291	2.7%	2.7%	2.7%
	Gender (% male)	90,219	74,144	43,075	57.1%	55.9%	55.8%
	Age (years) (sd)	90,219	74,144	43,075	59.8 (12.6)	62.7 (12.6)	65.4 (12.3)
	Duration of diabetes (years)	90,219	74,144	43,075	2.0	4.5	8.5
	Weight (kg) (sd)	79,724	65,208	38,272	89.9 (18.9)	87.7 (18.3)	86.7 (18.1)
	Height (cm) (sd)	40,453	39,072	22,887	168 (10)	168 (10)	168 (10)
Risk factors at diagnosis	Atrial fibrillation (%)	90,219	74,144	43,075	0.81%	0.78%	0.63%
	Peripheral vascular disease (%)	90,219	74,144	43,075	0.51%	0.53%	0.47%
	Smoking – current smoker (%)	63,779	47,682	21,759	19.1%	18.0%	19.0%
	Smoking – past smoker (%)	63,779	47,682	21,759	33.2%	33.6%	30.7%
	Total cholesterol (mmol/l) (sd)	65,553	49,441	22,928	5.27 (1.15)	5.31 (1.14)	5.49 (1.11)
	HD lipoprotein (mmol/l) (sd)	54,616	38,963	15,283	1.17 (0.30)	1.21 (0.30)	1.21 (0.30)
	Sys. blood pressure (mmHg) (sd)	72,999	56,515	29,152	139.6 (17.1)	141.3 (17.4)	143.2 (18.0)
	HbA1c (%) (sd)	63,370	46,993	21,749	8.2% (2.0)	7.8% (1.9)	7.9% (1.9%)
Current risk factors	Smoking – current smoker (%)	74,304	64,317	37,929	18.1%	15.1%	13.4%
	Smoking – past smoker (%)	74,304	64,317	37,929	34.0%	35.8%	36.4%
	Total cholesterol (mmol/l) (sd)	77,236	64,253	37,997	4.96 (1.15)	4.47 (1.01)	4.36 (0.99)
	HD lipoprotein (mmol/l) (sd)	64,784	57,341	34,311	1.18 (0.30)	1.23 (0.32)	1.23 (0.32)
	Sys. blood pressure (mmHg) (sd)	84,688	66,943	39,309	137.5 (16.3)	136.3 (15.5)	136.2 (15.6)
	HbA1c (%) (sd)	78,093	63,874	38,075	8.4% (1.8)	7.3% (1.4)	7.6% (1.5)
Years since pre-existing complications	Ischaemic Heart Disease (sd)	90,219	74,144	43,075	3.2 (3.7)	2.8 (1.4)	5.3 (2.6)
	Congestive Heart Failure (sd)	90,219	74,144	43,075	2.5 (3.0)	2.4 (1.4)	3.9 (2.6)
	Amputation (sd)	90,219	74,144	43,075	2.0 (2.8)	2.4 (1.5)	3.8 (2.8)

Category	Characteristic	Number of people			Value		
		Initial Therapy	First Intensification	Second Intensification	Initial Therapy	First Intensification	Second Intensification
	Blindness (sd)	90,219	74,144	43,075	2.3 (2.6)	2.5 (1.4)	4.8 (2.6)
	Renal failure (sd)	90,219	74,144	43,075	3.0 (3.3)	2.3 (1.4)	3.8 (2.5)
	Stroke (sd)	90,219	74,144	43,075	2.7 (3.5)	2.5 (1.5)	4.2 (2.7)
	Myocardial Infarction (sd)	90,219	74,144	43,075	2.9 (3.8)	2.6 (1.5)	4.6 (2.7)
People with pre-existing complications (% of people)	Ischaemic heart disease	90,219	74,144	43,075	2.7%	5.2%	9.7%
	Congestive heart failure	90,219	74,144	43,075	0.5%	1.2%	2.3%
	Amputation	90,219	74,144	43,075	0.1%	0.2%	0.4%
	Blindness	90,219	74,144	43,075	0.4%	1.4%	2.2%
	Renal failure	90,219	74,144	43,075	0.2%	0.5%	1.0%
	Stroke	90,219	74,144	43,075	0.5%	0.9%	1.8%
	Myocardial infarction	90,219	74,144	43,075	0.8%	1.4%	2.5%

(a) Not all variables are recorded for all people. Therefore, whilst the total number of people in the dataset is shown, each variable may have a different denominator
(b) Smoking percentages based on those people with a smoking status recorded
(c) Ethnicity data source: Health Survey for England 2009-2011
(d) THIN data as at 31 August 2013
(e) Standard deviation (sd) given where appropriate
(f) HbA1c required in percentages for model inputs. To convert to mmol/mol, see 3.3.2
(g) For definitions of variables, see appendix F.2 of this document

Table 21: Natural logarithm baseline characteristics

Category	Characteristic	Initial Therapy	First Intensification	Second Intensification
Risk factors at diagnosis	Total cholesterol (mmol/l) (sd)	1.64 (0.22)	1.65 (0.22)	1.68 (0.21)
	HD lipoprotein (mmol/l/) (sd)	0.13 (0.25)	0.16 (0.25)	0.16 (0.25)
	Sys. blood pressure (mmHg) (sd)	4.93 (0.12)	4.94 (0.12)	4.96 (0.13)
	HbA1c (%) (sd)	2.07 (0.22)	2.03 (0.23)	2.04 (0.23)
Current risk factors	Weight (kg) (sd)	4.48 (0.21)	4.45 (0.21)	4.44 (0.21)
	Total cholesterol (mmol/l) (sd)	1.57 (0.23)	1.47 (0.22)	1.45 (0.22)
	HD lipoprotein (mmol/l/) (sd)	0.13 (0.25)	0.17 (0.26)	0.18 (0.26)
	Sys. blood pressure (mmHg) (sd)	4.92 (0.12)	4.91 (0.11)	4.91 (0.11)
	HbA1c (%) (sd)	2.10 (0.21)	1.98 (0.18)	2.01 (0.18)

(a) full dataset used

Table 22: Health Survey for England 2009-11 - weighted summary characteristics of people with type 2 diabetes

Category	Variable	Value
Demographics	Number of people	1291
	Ethnicity – White	94.6%
	Ethnicity – Afro-Caribbean	2.7%
	Ethnicity – Asian-Indian	2.7%
	Gender (% male)	56.3%
	Age (years)	64.2
	Duration of diabetes (years)	8.8
	Weight (kg)	88.2
	Height (cm)	166
Current Risk Factor	Smoking – current smoker (%)	15.5%
	Smoking – past smoker (%)	40.6%
	Total cholesterol (mmol/l)	4.46
	HD lipoprotein (mmol/l)	1.27
	Sys. blood pressure (mmHg)	133.3
	HbA1c (%)	7.5%

(a) Note, apart from ethnicity categories, these summary data were not used in the original health economic model. They are included here for comparison to the THIN dataset used only
(b) Not all variables are recorded for all people.. Therefore, whilst the total number of people in the dataset is shown, each variable may have a different denominator
(c) HbA1c required in percentages for model inputs. To convert to mmol/mol, see 3.3.2
(d) Where a variable is not shown in the table, it was not available in the HSE dataset
(e) For definitions of variables, see appendix F.2 of this document

Table 23: Health Survey for England 2009-11 - weighted ethnicity correlation data

Variable	Correlation
Gender	0.042
Smoking	-0.151
Total Cholesterol (natural logarithm)	0.003
HD lipoprotein (natural logarithm)	-0.121
Sys. blood pressure (natural logarithm)	-0.047
HbA1c Log	0.127

(a) Ethnicity correlations for age, diabetes duration, weight, height not used

Table 24: Correlations between baseline characteristic variables - initial therapy

	Gen	Age	Dur	Wei	Hei	Smo	Cho	HDL	SBP	HbA	*AF*	*PVD*	*Smo*	*Cho*	*HDL*	*SBP*	*HbA*	IHD	CHF	Amp	ESRF	Str	MI	Bli
Gender	1.00	0.07	0.01	-0.24	-0.71	-0.14	0.10	0.27	-0.01	-0.06	0.00	-0.03	-0.14	0.11	0.27	-0.01	-0.07	-0.03	0.00	-0.01	0.00	-0.01	-0.02	0.02
Age	0.07	1.00	0.18	-0.27	-0.15	-0.06	-0.19	0.22	0.16	-0.14	0.07	0.04	-0.06	-0.14	0.22	0.18	-0.17	0.06	0.05	0.01	0.03	0.02	0.03	0.03
Duration	0.01	0.18	1.00	-0.01	-0.02	-0.03	-0.17	0.04	-0.02	-0.07	-0.01	0.00	-0.02	0.01	0.05	0.05	-0.30	0.12	0.07	0.03	0.05	0.03	0.06	0.11
Weight*	-0.24	-0.27	-0.01	1.00	0.45	0.07	-0.02	-0.26	0.06	-0.02	-0.02	-0.01	0.07	-0.04	-0.26	0.05	-0.04	-0.02	0.01	0.01	0.00	0.00	-0.01	-0.02
Height	-0.71	-0.15	-0.02	0.45	1.00	0.14	-0.04	-0.23	0.00	0.07	0.01	0.02	0.13	-0.06	-0.23	0.01	0.07	0.01	0.00	0.01	-0.01	0.01	0.01	-0.02
Smoking	-0.14	-0.06	-0.03	0.07	0.14	1.00	0.02	-0.14	-0.02	0.01	-0.01	0.06	0.96	0.02	-0.13	-0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.01	-0.01
Chol*	0.10	-0.19	-0.17	-0.02	-0.04	0.02	1.00	0.16	0.09	0.20	-0.05	-0.02	0.02	0.81	0.14	0.06	0.23	-0.09	-0.02	-0.02	-0.01	-0.03	-0.05	-0.02
HDL*	0.27	0.22	0.04	-0.26	-0.23	-0.14	0.16	1.00	0.05	-0.07	0.00	-0.01	-0.14	0.17	0.94	0.05	-0.07	-0.01	0.01	-0.01	-0.01	-0.01	-0.02	0.01
SBP*	-0.01	0.16	-0.02	0.06	0.00	-0.02	0.09	0.05	1.00	0.03	-0.02	0.01	-0.02	0.08	0.05	0.77	0.03	-0.02	-0.01	0.00	0.00	0.01	-0.02	0.00
HbA1c*	-0.06	-0.14	-0.07	-0.02	0.07	0.01	0.20	-0.07	0.03	1.00	-0.03	0.00	0.02	0.18	-0.07	0.03	0.89	-0.03	-0.01	0.00	-0.01	0.00	-0.02	0.00
AF	0.00	0.07	-0.01	-0.02	0.01	-0.01	-0.05	0.00	-0.02	-0.03	1.00	0.00	-0.01	-0.05	0.00	-0.01	-0.02	0.00	0.02	0.00	0.00	0.00	0.01	0.02
PVD	-0.03	0.04	0.00	-0.01	0.02	0.06	-0.02	-0.01	0.01	0.00	0.00	1.00	0.05	-0.01	-0.01	0.01	0.00	0.03	0.03	0.00	0.02	0.00	0.03	0.01
Smoking	-0.14	-0.06	-0.02	0.07	0.13	0.96	0.02	-0.14	-0.02	0.02	-0.01	0.05	1.00	0.02	-0.13	-0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.02	0.00
Total Chol*	0.11	-0.14	0.01	-0.04	-0.06	0.02	0.81	0.17	0.08	0.18	-0.05	-0.01	0.02	1.00	0.18	0.10	0.18	-0.04	-0.01	-0.01	-0.01	-0.01	-0.03	0.01
HDL*	0.27	0.22	0.05	-0.26	-0.23	-0.13	0.14	0.94	0.05	-0.07	0.00	-0.01	-0.13	0.18	1.00	0.06	-0.07	0.00	0.01	-0.01	-0.01	-0.01	-0.02	0.01
SBP*	-0.01	0.18	0.05	0.05	0.01	-0.03	0.06	0.05	0.77	0.03	-0.01	0.01	-0.03	0.10	0.06	1.00	0.02	0.01	0.00	0.00	0.01	0.02	0.00	0.02
HbA1c*	-0.07	-0.17	-0.30	-0.04	0.07	0.01	0.23	-0.07	0.03	0.89	-0.02	0.00	0.01	0.18	-0.07	0.02	1.00	-0.05	-0.02	-0.01	-0.02	-0.01	-0.03	-0.03
IHD	-0.03	0.06	0.12	-0.02	0.01	0.00	-0.09	-0.01	-0.02	-0.03	0.00	0.03	0.00	-0.04	0.00	0.01	-0.05	1.00	0.08	0.00	0.02	0.00	0.14	0.01
CHF	0.00	0.05	0.07	0.01	0.00	0.00	-0.02	0.01	-0.01	-0.01	0.02	0.03	0.00	-0.01	0.01	0.00	-0.02	0.08	1.00	0.00	0.00	0.03	0.03	0.00
Amp	-0.01	0.01	0.03	0.01	0.01	0.00	-0.02	-0.01	0.00	0.00	0.00	0.00	0.00	-0.01	-0.01	0.00	-0.01	0.00	0.00	1.00	0.00	0.00	0.00	0.00
ESRF	0.00	0.03	0.05	0.00	-0.01	0.00	-0.01	-0.01	0.00	-0.01	0.00	0.02	0.00	-0.01	-0.01	0.01	-0.02	0.02	0.00	0.00	1.00	0.00	0.00	0.00
Stroke	-0.01	0.02	0.03	0.00	0.01	0.00	-0.03	-0.01	0.01	0.00	0.00	0.00	0.00	-0.01	-0.01	0.02	-0.01	0.00	0.03	0.00	0.00	1.00	0.00	0.00
MI	-0.02	0.03	0.06	-0.01	0.01	0.01	-0.05	-0.02	-0.02	-0.02	0.01	0.03	0.02	-0.03	-0.02	0.00	-0.03	0.14	0.03	0.00	0.00	0.00	1.00	0.01
Blind	0.02	0.03	0.11	-0.02	-0.02	-0.01	-0.02	0.01	0.00	0.00	0.02	0.01	0.00	0.01	0.01	0.02	-0.03	0.01	0.00	0.00	0.00	0.00	0.01	1.00

*(a) * deontes logged variable*
(b) Italics denote variable at diagnosis
(c) Null values excluded from analysis
(d) Due to space restrictions, only first 3 characters of column titles shown. Note that fuller titles are shown in row headers
(e) Chol = total cholesterol, HDL = high density lipoprotein, SBP = systolic blood pressure, AF = atrial fibrillation, PVD = peripheral vascular disease, IHD = ischaemic heart disease, CHF = congestive heart failure, Amp = amputation, ESRF = end stage renal failure, MI = myocardial infarction, Blind = blindness

Table 25: Correlations between baseline characteristic variables - first intensification of therapy

	Gen	Age	Dur	Wei	Hei	Smo	Cho	HDL	SBP	HbA	*AF*	*PVD*	*Smo*	*Cho*	*HDL*	*SBP*	*HbA*	IHD	CHF	Amp	ESRF	Str	MI	Bli
Gender	1.00	0.06	.	-0.30	-0.72	-0.15	0.17	0.28	0.00	-0.04	0.00	-0.02	-0.15	0.13	0.26	0.00	-0.04	-0.05	-0.02	-0.01	0.01	-0.01	-0.04	0.01
Age	0.06	1.00	.	-0.33	-0.16	-0.05	-0.09	0.20	0.13	-0.25	0.07	0.04	-0.06	-0.14	0.22	0.17	-0.16	0.07	0.08	0.02	0.06	0.03	0.03	0.05
Duration	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Weight*	-0.30	-0.33	.	1.00	0.48	0.07	-0.04	-0.29	0.05	0.16	-0.01	-0.02	0.07	-0.03	-0.25	0.02	0.05	-0.01	0.01	0.01	-0.03	-0.02	0.00	-0.02
Height	-0.72	-0.16	.	0.48	1.00	0.12	-0.12	-0.24	-0.01	0.07	0.01	0.01	0.12	-0.08	-0.22	-0.01	0.05	0.01	0.00	0.01	-0.03	0.00	0.02	-0.02
Smoking	-0.15	-0.05	.	0.07	0.12	1.00	0.00	-0.12	-0.01	0.03	-0.02	0.05	0.79	-0.01	-0.13	-0.02	0.03	0.02	0.00	0.01	-0.01	0.01	0.03	0.01
Chol*	0.17	-0.09	.	-0.04	-0.12	0.00	1.00	0.24	0.07	0.11	-0.03	-0.02	-0.01	0.31	0.16	-0.01	-0.05	-0.05	-0.01	0.00	0.02	-0.03	-0.04	-0.01
HDL*	0.28	0.20	.	-0.29	-0.24	-0.12	0.24	1.00	0.04	-0.19	-0.01	0.00	-0.12	0.13	0.71	0.05	-0.09	-0.04	-0.01	0.00	0.00	-0.01	-0.04	0.00
SBP*	0.00	0.13	.	0.05	-0.01	-0.01	0.07	0.04	1.00	0.03	-0.01	0.01	-0.02	0.05	0.05	0.27	0.00	-0.02	-0.03	0.00	0.01	-0.02	-0.01	0.01
HbA1c*	-0.04	-0.25	.	0.16	0.07	0.03	0.11	-0.19	0.03	1.00	0.00	-0.03	0.04	0.07	-0.10	-0.04	0.33	0.00	0.00	0.00	-0.02	-0.01	0.01	-0.01
AF	0.00	0.07	.	-0.01	0.01	-0.02	-0.03	-0.01	-0.01	0.00	1.00	0.03	-0.02	-0.06	-0.01	-0.03	-0.02	0.02	0.06	0.00	0.00	0.00	0.02	0.00
PVD	-0.02	0.04	.	-0.02	0.01	0.05	-0.02	0.00	0.01	-0.03	0.03	1.00	0.05	-0.02	0.00	0.00	-0.02	0.05	0.04	0.00	0.02	0.00	0.05	0.01
Smoking	-0.15	-0.06	.	0.07	0.12	0.79	-0.01	-0.12	-0.02	0.04	-0.02	0.05	1.00	0.01	-0.13	-0.03	0.03	0.02	0.00	0.01	-0.01	0.02	0.04	0.01
Total Chol*	0.13	-0.14	.	-0.03	-0.08	-0.01	0.31	0.13	0.05	0.07	-0.06	-0.02	0.01	1.00	0.18	0.11	0.16	-0.07	-0.05	-0.01	-0.02	-0.02	-0.03	-0.01
HDL*	0.26	0.22	.	-0.25	-0.22	-0.13	0.16	0.71	0.05	-0.10	-0.01	0.00	-0.13	0.18	1.00	0.07	-0.10	-0.02	0.00	-0.01	0.00	-0.01	-0.03	0.00
SBP*	0.00	0.17	.	0.02	-0.01	-0.02	-0.01	0.05	0.27	-0.04	-0.03	0.00	-0.03	0.11	0.07	1.00	0.01	0.01	0.00	-0.01	0.02	0.01	0.01	0.00
HbA1c*	-0.04	-0.16	.	0.05	0.05	0.03	-0.05	-0.09	0.00	0.33	-0.02	-0.02	0.03	0.16	-0.10	0.01	1.00	-0.02	-0.01	0.00	-0.02	-0.01	0.00	0.00
IHD	-0.05	0.07	.	-0.01	0.01	0.02	-0.05	-0.04	-0.02	0.00	0.02	0.05	0.02	-0.07	-0.02	0.01	-0.02	1.00	0.08	0.00	0.02	0.02	0.17	0.01
CHF	-0.02	0.08	.	0.01	0.00	0.00	-0.01	-0.01	-0.03	0.00	0.06	0.04	0.00	-0.05	0.00	0.00	-0.01	0.08	1.00	0.00	0.04	0.02	0.08	0.00
Amp	-0.01	0.02	.	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.01	-0.01	-0.01	-0.01	0.00	0.00	0.00	1.00	0.03	0.00	0.00	0.00
ESRF	0.01	0.06	.	-0.03	-0.03	-0.01	0.02	0.00	0.01	-0.02	0.00	0.02	-0.01	-0.02	0.00	0.02	-0.02	0.02	0.04	0.03	1.00	0.02	0.03	0.02
Stroke	-0.01	0.03	.	-0.02	0.00	0.01	-0.03	-0.01	-0.02	-0.01	0.00	0.00	0.02	-0.02	-0.01	0.01	-0.01	0.02	0.02	0.00	0.02	1.00	0.02	0.01
MI	-0.04	0.03	.	0.00	0.02	0.03	-0.04	-0.04	-0.01	0.01	0.02	0.05	0.04	-0.03	-0.03	0.01	0.00	0.17	0.08	0.00	0.03	0.02	1.00	0.00
Blind	0.01	0.05	.	-0.02	-0.02	0.01	-0.01	0.00	0.01	-0.01	0.00	0.01	0.01	-0.01	0.00	0.00	0.00	0.01	0.00	0.00	0.02	0.01	0.00	1.00

*(a) * deontes logged variable*
(b) Italics denote variable at diagnosis
(c) Null values excluded from analysis
(d) Due to space restrictions, only first 3 characters of column titles shown. Note that fuller titles are shown in row headers
(e) Chol = total cholesterol, HDL = high density lipoprotein, SBP = systolic blood pressure, AF = atrial fibrillation, PVD = peripheral vascular disease, IHD = ischaemic heart disease, CHF = congestive heart failure, Amp = amputation, ESRF = end stage renal failure, MI = myocardial infarction, Blind = blindness
(f) As data were selected based on disease duration, this variable was not included in the analysis

Table 26: Correlations between baseline characteristic variables - second intensification of therapy

	Gen	Age	Dur	Wei	Hei	Smo	Cho	HDL	SBP	HbA	*AF*	*PVD*	*Smo*	*Cho*	*HDL*	*SBP*	*HbA*	IHD	CHF	Amp	ESRF	Str	MI	Bli
Gender	1.00	0.05	.	-0.31	-0.71	-0.13	0.20	0.30	0.02	-0.02	0.01	-0.03	-0.14	0.11	0.25	0.00	-0.04	-0.06	-0.01	-0.01	0.01	-0.01	-0.05	0.00
Age	0.05	1.00	.	-0.33	-0.17	-0.07	-0.06	0.16	0.09	-0.28	0.06	0.02	-0.08	-0.10	0.22	0.20	-0.13	0.10	0.10	0.00	0.06	0.04	0.03	0.08
Duration	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Weight*	-0.31	-0.33	.	1.00	0.48	0.06	-0.07	-0.28	0.03	0.19	-0.02	-0.01	0.07	-0.03	-0.24	0.01	0.06	-0.01	0.03	0.00	-0.03	0.00	-0.01	-0.02
Height	-0.71	-0.17	.	0.48	1.00	0.11	-0.13	-0.25	-0.01	0.05	-0.01	0.03	0.12	-0.08	-0.23	-0.03	0.06	0.00	0.01	0.02	-0.04	0.00	0.03	-0.02
Smoking	-0.13	-0.07	.	0.06	0.11	1.00	-0.03	-0.12	-0.04	0.03	-0.03	0.06	0.75	0.02	-0.14	-0.04	0.02	0.03	0.00	0.00	0.00	0.01	0.04	0.00
Chol*	0.20	-0.06	.	-0.07	-0.13	-0.03	1.00	0.25	0.09	0.11	-0.02	0.00	-0.02	0.24	0.14	0.01	-0.05	-0.04	-0.04	0.02	0.01	0.00	-0.03	-0.02
HDL*	0.30	0.16	.	-0.28	-0.25	-0.12	0.25	1.00	0.03	-0.20	-0.04	-0.01	-0.12	0.13	0.64	0.03	-0.06	-0.04	-0.05	-0.03	-0.01	-0.01	-0.06	0.00
SBP*	0.02	0.09	.	0.03	-0.01	-0.04	0.09	0.03	1.00	0.06	0.02	0.01	-0.04	0.05	0.03	0.20	0.01	-0.03	-0.06	0.02	0.02	0.00	-0.03	0.01
HbA1c*	-0.02	-0.28	.	0.19	0.05	0.03	0.11	-0.20	0.06	1.00	-0.01	-0.01	0.04	0.06	-0.09	-0.06	0.24	-0.03	0.02	0.00	-0.01	-0.01	0.01	-0.01
AF	0.01	0.06	.	-0.02	-0.01	-0.03	-0.02	-0.04	0.02	-0.01	1.00	-0.01	-0.03	-0.05	-0.02	-0.02	0.00	0.00	0.07	-0.01	-0.01	0.01	-0.01	0.01
PVD	-0.03	0.02	.	-0.01	0.03	0.06	0.00	-0.01	0.01	-0.01	-0.01	1.00	0.07	-0.02	0.00	-0.01	-0.03	0.05	0.00	-0.01	0.03	0.02	0.05	-0.02
Smoking	-0.14	-0.08	.	0.07	0.12	0.75	-0.02	-0.12	-0.04	0.04	-0.03	0.07	1.00	0.05	-0.13	-0.03	0.03	0.04	-0.01	0.01	0.01	0.00	0.06	-0.01
Total Chol*	0.11	-0.10	.	-0.03	-0.08	0.02	0.24	0.13	0.05	0.06	-0.05	-0.02	0.05	1.00	0.19	0.13	0.12	-0.09	-0.08	0.02	-0.01	-0.01	-0.02	-0.01
HDL*	0.25	0.22	.	-0.24	-0.23	-0.14	0.14	0.64	0.03	-0.09	-0.02	0.00	-0.13	0.19	1.00	0.07	-0.07	-0.02	-0.01	-0.01	0.01	-0.02	-0.03	0.00
SBP*	0.00	0.20	.	0.01	-0.03	-0.04	0.01	0.03	0.20	-0.06	-0.02	-0.01	-0.03	0.13	0.07	1.00	0.00	-0.02	-0.02	0.00	0.01	0.02	0.00	0.02
HbA1c*	-0.04	-0.13	.	0.06	0.06	0.02	-0.05	-0.06	0.01	0.24	0.00	-0.03	0.03	0.12	-0.07	0.00	1.00	-0.03	0.01	-0.01	-0.03	-0.02	0.00	0.01
IHD	-0.06	0.10	.	-0.01	0.00	0.03	-0.04	-0.04	-0.03	-0.03	0.00	0.05	0.04	-0.09	-0.02	-0.02	-0.03	1.00	0.10	0.02	0.06	0.04	0.19	0.02
CHF	-0.01	0.10	.	0.03	0.01	0.00	-0.04	-0.05	-0.06	0.02	0.07	0.00	-0.01	-0.08	-0.01	-0.02	0.01	0.10	1.00	0.06	0.06	0.03	0.10	0.01
Amp	-0.01	0.00	.	0.00	0.02	0.00	0.02	-0.03	0.02	0.00	-0.01	-0.01	0.01	0.02	-0.01	0.00	-0.01	0.02	0.06	1.00	-0.01	-0.01	0.07	0.01
ESRF	0.01	0.06	.	-0.03	-0.04	0.00	0.01	-0.01	0.02	-0.01	-0.01	0.03	0.01	-0.01	0.01	0.01	-0.03	0.06	0.06	-0.01	1.00	0.00	0.03	0.01
Stroke	-0.01	0.04	.	0.00	0.00	0.01	0.00	-0.01	0.00	-0.01	0.01	0.02	0.00	-0.01	-0.02	0.02	-0.02	0.04	0.03	-0.01	0.00	1.00	-0.01	0.02
MI	-0.05	0.03	.	-0.01	0.03	0.04	-0.03	-0.06	-0.03	0.01	-0.01	0.05	0.06	-0.02	-0.03	0.00	0.00	0.19	0.10	0.07	0.03	-0.01	1.00	0.00
Blind	0.00	0.08	.	-0.02	-0.02	0.00	-0.02	0.00	0.01	-0.01	0.01	-0.02	-0.01	-0.01	0.00	0.02	0.01	0.02	0.01	0.01	0.01	0.02	0.00	1.00

*(a) * deontes logged variable*
(b) Italics denote variable at diagnosis
(c) Null values excluded from analysis
(d) Due to space restrictions, only first 3 characters of column titles shown. Note that fuller titles are shown in row headers
(e) Chol = total cholesterol, HDL = high density lipoprotein, SBP = systolic blood pressure, AF = atrial fibrillation, PVD = peripheral vascular disease, IHD = ischaemic heart disease, CHF = congestive heart failure, Amp = amputation, ESRF= end stage renal failure, MI = myocardial infarction, Blind = blindness
(a) As data were selected based on disease duration, this variable was not included in the analysis

3.4 Comparators modelled

As well as only modelling treatments which reported HbA1c at 1 year, a further limitation on treatments that could be included in the original health economic model was the requirement for data to be available on all relevant treatment effects. This in effect created a minimum dataset for each treatment to be included of HbA1c at 1 year, weight-change at 1 year, hypoglycaemia rates and treatment dropouts due to intolerance.

Whilst this could be seen as a weakness of the original health economic model, the GDG were happy that the majority of the key comparators were included. Estimating missing data items to increase the number of treatment options modelled would have introduced unnecessary uncertainty. It should be noted that the original health economic model covered more treatment options than any previous analysis found.

3.4.1 Initial therapy

We were able to model 7 out of 12 initial therapy treatment options for which there was some included clinical evidence (see table 27).

Table 27: Comparators modelled and not modelled - initial therapy

Modelled	Not modelled
Metformin	Acarbose
Pioglitazone	Linagliptin
Placebo	Metformin (modified release)
Repaglinide	Saxagliptin
Sitagliptin	Sulfonylurea (modified release)
Sulfonylurea	
Vildagliptin	

3.4.2 First intensification

We were able to model 7 out of 14 first intensification treatment options for which there was some included clinical evidence (see table 28). All treatment options modelled at first intensification included metformin and no treatment options included a meglitinide.

Table 28: Comparators modelled and not modelled - first intensification of therapy

Modelled	Not modelled
Exenatide-metformin	Acarbose-metformin
Linagliptin-metformin	Lixisenatide-metformin
Liraglutide-metformin	Metformin-nateglinide
Metformin-pioglitazone	Metformin-saxagliptin
Metformin-sitagliptin	Pioglitazone-sitagliptin
Metformin-sulfonylurea	Pioglitazone-sulfonylurea
Metformin-vildagliptin	Sitagliptin-sulfonylurea

3.4.3 Second intensification

We were able to model 20 out of 32 second intensification treatment options for which there was some included clinical evidence (see table 29). The modelled treatment options included combinations of 3 oral anti-diabetes drugs, insulins (long acting and biphasic) with and without oral anti-diabetes drugs and GLP-1 agonists with oral anti-diabetes drugs. The

clinical NMAs for second intensification were less well linked than for initial therapy and first intensification.

Table 29: Comparators modelled and not modelled - second intensification of therapy

Modelled	Not modelled
Biphasic insulin aspart-metformin	Acarbose-metformin-sulfonylurea
Biphasic insulin aspart-metformin-sulfonylurea	Biphasic human insulin-NPH insulin
Biphasic insulin aspart-repaglinide	Biphasic insulin aspart
Exenatide-metformin-sulfonylurea	Biphasic insulin aspart-pioglitazone
Insulin degludec/aspart mix-metformin	Insulin aspart (short acting)
Insulin degludec-metformin	Insulin aspart (short acting)-metformin
Insulin detemir-metformin	Insulin lispro mix 75/25-metformin
Insulin glargine-metformin	Metformin-NPH insulin mix 70/30
Insulin glargine-metformin-sulfonylurea	Metformin-repaglinide-sulfonylurea
Insulin glargine-sulfonylurea	NPH insulin mix 70/30
Insulin lispro mix 50 and mix 25	NPH insulin mix 70/30-sulfonylurea
Insulin lispro mix 50/50-metformin	NPH insulin-repaglinide
Liraglutide-metformin-sulfonylurea	
Metformin-NPH insulin	
Metformin-NPH insulin-repaglinide	
Metformin-NPH insulin-sulfonylurea	
Metformin-pioglitazone-sulfonylurea	
Metformin-sitagliptin-sulfonylurea	
NPH insulin	
NPH insulin-sulfonylurea	

3.5 Treatment effect derivation

Each of the 4 safety and efficacy parameters on which the original health economic model relied comprised 2 elements: an estimate of relative effect, drawn from the relevant NMAs in the effectiveness review, and an estimate of absolute ('baseline') effect. Put more simply, the NMAs told us how much **more** or **less** likely people were to experience the event of interest, given the treatment to which they had been assigned, but additional evidence is necessary to estimate 'more likely than **what**?'

There are several options for estimating baseline effects, amongst which 2 key approaches are:

(1) to seek an estimate of underlying event-rate from epidemiological literature external to the included safety and efficacy studies, and

(2) to pool observed effects in the individual arms of included RCTs that relate to the reference comparator (Dias et al. 2011b).

We used both approaches in our model. For incidence of hypoglycaemic events, we used external epidemiological literature (see 3.5.4). For HbA1c, weight and dropouts due to adverse events, we synthesised relevant data from included RCTs. To do this, we followed the recommendations of the NICE decision support unit technical support document 5 (NICE DSU TSD5) (Dias et al. 2011b), combining data using the same Bayesian Generalised Linear Modelling framework that was used in the NMAs of treatment effect. Syntheses were

performed in WinBUGS, with 3 chains performing 50,000 'burn-in' iterations that were discarded and followed by 10,000 iterations from which posterior distributions were recorded. WinBUGS code for these analyses is given in Appendix K of the main guideline. The choice between fixed- and random-effects approaches was dictated by the model that had been found to be superior in the corresponding relative effects analysis (NMA). It would have been possible to discriminate between baseline models on the basis of their fit to the baseline data; however, we chose not to do this, as it may have led to a situation where one comparator in the network was based on a fixed-effects model (and, hence, would have a fairly narrow estimate of uncertainty around its treatment effect), whereas all other options were based on a random-effects NMA allied to this baseline effect (with much wider range of uncertainty). We took the view that this would be unhelpful, not least because the choice of baseline treatment (which is, under normal circumstances, arbitrary) would become very important, and there would be no objective way of making that choice.

3.5.1 HbA1c

Because it is a continuous measure, HbA1c effects are estimated on a natural scale to be a combination of baseline value, 1-year effect with the reference comparator and 1-year effectiveness of the treatment in question compared with the reference comparator.

Expressed algebraically, HbA1c at 1 year with treatment i ($H_{1,i}$) equates to baseline HbA1c (H_0) plus the amount HbA1c is expected to change after 1 year on the reference treatment ($c_{1,1}$) plus the extent to which treatment i is better or worse than the reference treatment ($d_{1,1i}$):

$$H_{1,i} = H_0 + c_{1,1} + d_{1,1i} \quad \textbf{(1)}$$

For each simulated individual, the model samples a value of H_0 when each model-run is initiated (see 3.2.1); $c_{1,1}$ is drawn from the baseline model (see below); $d_{1,1i}$ is taken from the NMA (see section 8.4 in the main guideline).

3.5.1.1 Initial therapy

For initial therapy, the reference option in the network was metformin. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.1.1), 8 metformin arms from 7 studies reported change in HbA1c at 1 year. In preliminary analysis, we noted that there appeared to be a strong correlation between baseline HbA1c and change in HbA1c at 1 year (see figure 9).

Therefore, we explored the inclusion of baseline HbA1c as a covariate in our synthesis model, to adjust for this effect. In this analysis, model **(1)** was extended such that

$$H_{1,i} = H_0 + c_{1,1} + \beta(H_0 - 7.5) + d_{1,1i} \quad \textbf{(2)}$$

, where β is a coefficient estimating the extent to which the 1-year change with metformin would be expected to increase or decrease for every unit of baseline HbA1c above or below 7.5%. Analyses were centred around 7.5% as this was likely to be close to the mean of values in the dataset (thus making the analysis computationally more efficient) and it also provided conveniently interpretable outputs.

Because the random-effects NMA was selected as having a better fit to the data, we ran the baseline models with a random-effects term. It was given a noninformative U(0,5) prior. The beta coefficient was also given a noninformative U(0,10^{-4}) prior.

Model outputs are shown in table 30.

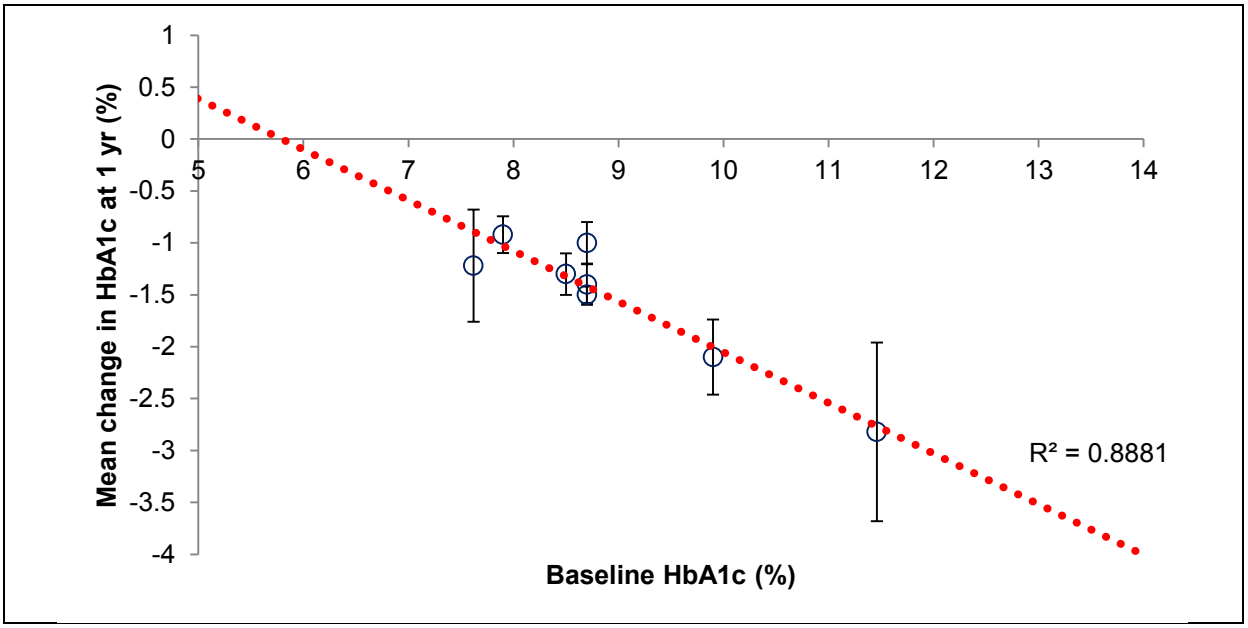


Figure 9: Relationship between baseline HbA1c and change in HbA1c at 1 year – metformin as initial therapy

Table 30: Baseline synthesis model: change in HbA1c (%) at 1 year – metformin as initial therapy

		Unadjusted model – median (95%CrI)	Adjusted for baseline HbA1c – median (95%CrI)
1-year change with metformin	predicted	-1.49 (-3.27, 0.21)	-0.78 (-1.65, 0.03)
	mean	-1.49 (-2.16, -0.90)	-0.78 (-1.28, -0.33)
tau		0.65 (0.31, 1.61)	0.25 (0.10, 0.77)
beta		–	-0.50 (-0.78, -0.21)
DIC		-0.490	-2.134

We concluded that the adjusted baseline model had a superior fit to the data. Although difference in DIC was relatively small between the 2 models, the adjusted model had a lower value, indicating superior fit (it should also be noted that the inclusion of a random-effects term will very much reduce the ability to discriminate between models; indeed, although fixed-effects versions of the same analysis would not be preferred due to much higher DIC, it was notable that the difference between the unadjusted [DIC=62.10] and adjusted [DIC=12.35] models was stark). Other reasons for preferring the adjusted model are that the coefficient itself is estimated to be unambiguously influential (its credible interval does not cross 0) and the reduction in the inter-study SD, indicating that baseline HbA1c explains much of the heterogeneity in observed 1-year changes in HbA1c.

For these reasons, the health economic model used the adjusted baseline synthesis model to estimate 1-year change in HbA1c, using the approach specified in equation **(2)**. To give a worked example, an individual with a sampled baseline HbA1c of 8% who received pioglitazone (which is estimated, in the relevant NMA to result in HbA1c 0.039% higher at 1 year than in people taking metformin) would have their 1-year HbA1c estimated as follows:

$$H_{1,i} = 8 - 0.78 - 0.50(8 - 7.5) + 0.039$$

$$= 7.009$$

3.5.1.2 First intensification

The reference option in the first intensification network was metformin-sulfonylurea. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.2.1), 13 metformin-sulfonylurea arms from 13 studies reported change in HbA1c at 1 year. Again, we noted a correlation between baseline HbA1c and change in HbA1c at 1 year (see figure 10), and explored the inclusion of a covariate in our synthesis model, to adjust for this effect.

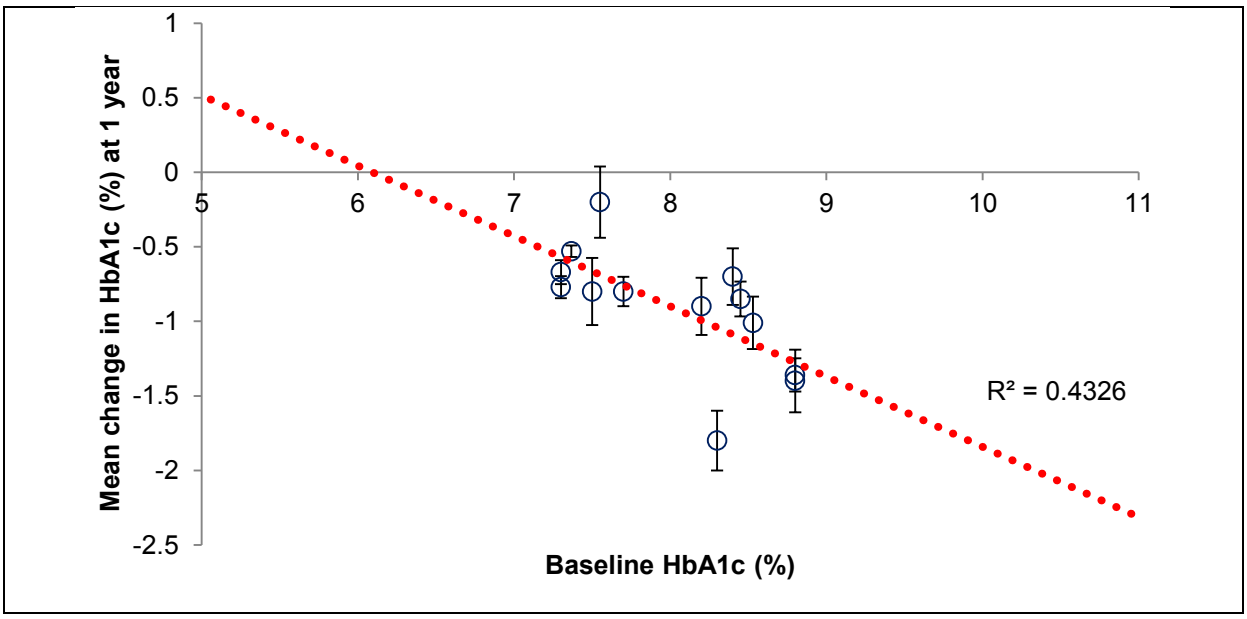


Figure 10: Relationship between baseline HbA1c and change in HbA1c at 1 year – metformin-sulfonylurea at first intensification

Because the random-effects NMA was selected as having a better fit to the data, we ran the baseline models with a random-effects term. It was given a noninformative U(0,5) prior.

Model outputs are shown in table 31.

Table 31: Baseline synthesis model: change in HbA1c (%) at 1 year – metformin-sulfonylurea at first intensification

		Unadjusted model – median (95%CrI)	Adjusted for baseline HbA1c – median (95%CrI)
1-year change with metformin-sulfonylurea	predicted	-0.91 (-1.86, 0.04)	-0.67 (-1.43, 0.10)
	mean	-0.91 (-1.16, -0.65)	-0.67 (-0.95, -0.39)
tau		0.43 (0.28, 0.71)	0.33 (0.21, 0.58)
beta		–	-0.46 (-0.84, -0.10)
DIC		-19.919	-19.897

It is not possible to discriminate between these models on the basis of DIC; however, the credible interval for the coefficient does not cross 0 and inter-study SD is somewhat reduced,

indicating that baseline HbA1c explains some of the heterogeneity in observed 1-year changes in HbA1c. Again, we recognise that the inclusion of a random-effects term attenuates differences between models, and note that there was a conspicuous difference between the unadjusted and adjusted models in fixed-effects analyses (367.49 versus 118.86).

For these reasons, the health economic model used the adjusted baseline synthesis model to estimate 1-year change in HbA1c, using the approach specified in equation **(2)**. To give a worked example, an individual with a sampled baseline HbA1c of 8% who received liraglutide-metformin (which is estimated, in the relevant NMA to result in HbA1c 0.144% lower at 1 year than in people taking metformin-sulfonylurea) would have their 1-year HbA1c estimated as follows:

$$H_{1,i} = 8 - 0.67 - 0.46(8 - 7.5) - 0.144$$

$$= 6.956$$

3.5.1.3 Second intensification

The reference option in the second intensification network was insulin glargine-metformin. This represents a departure from the NMA reported in the main guideline, in which metformin-NPH insulin is reported as reference option for interpretability's sake. The relative treatment effects are entirely unaffected by this change, as the choice of reference comparator is mathematically arbitrary (Dias et al. 2011a); however, there are slightly more data for insulin glargine-metformin, which is useful for the purposes of estimating baseline effects.

In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.3.1), 8 insulin glargine-metformin arms from 8 studies reported change in HbA1c at up to 1 year. Again, we noted a correlation between baseline HbA1c and change in HbA1c at up to 1 year (see figure 11), and explored the inclusion of a covariate in our synthesis model, to adjust for this effect.

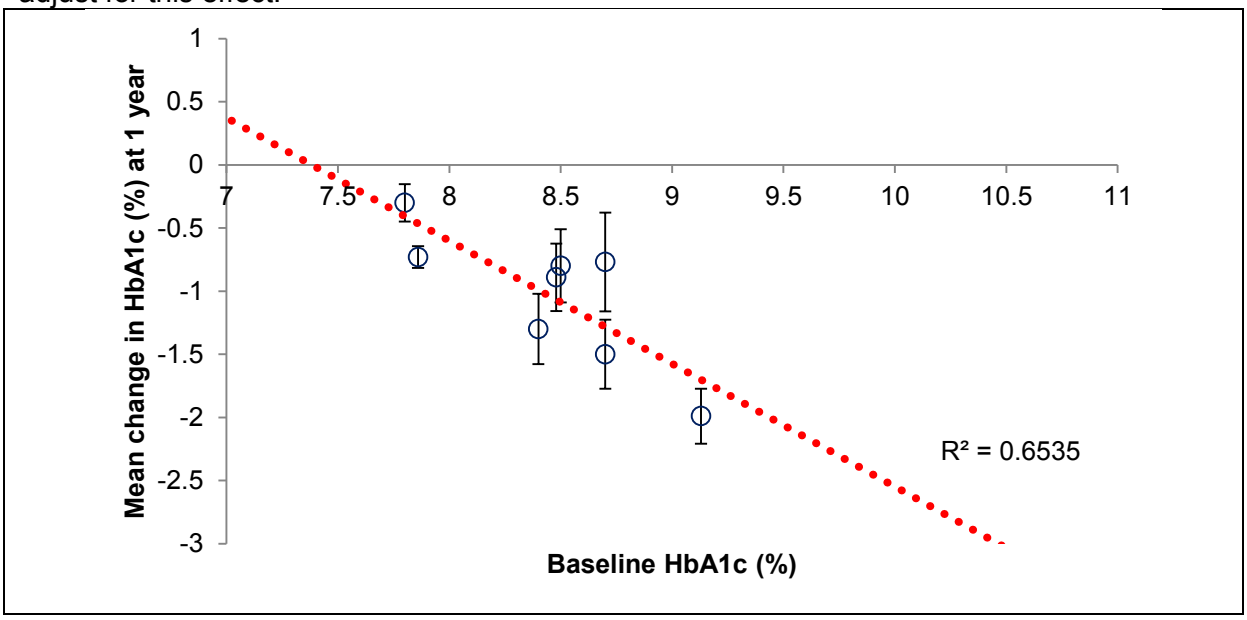


Figure 11: Relationship between baseline HbA1c and change in HbA1c at up to 1 year – insulin glargine-metformin at second intensification

Because the random-effects NMA was selected as having a better fit to the data, we ran the baseline models with a random-effects term. It was given a noninformative U(0,5) prior.

Model outputs are shown in table 32.

Table 32: Baseline synthesis model: change in HbA1c (%) at up to 1 year – insulin glargine-metformin at second intensification

		Unadjusted model – median (95%CrI)	Adjusted for baseline HbA1c – median (95%CrI)
1-year change with insulin glargine-metformin	predicted	-1.03 (-2.50, 0.45)	-0.12 (-1.29, 1.03)
	mean	-1.03 (-1.53, -0.53)	-0.12 (-0.88, 0.63)
tau		0.60 (0.36, 1.27)	0.35 (0.17, 0.85)
beta			-0.98 (-1.70, -0.23)
DIC		-4.405	-4.156

The situation, here, is very similar to that for first intensification: it is not possible to discriminate between these models on the basis of DIC, but the credible interval for the coefficient does not cross 0 and inter-study SD is clearly reduced, indicating that baseline HbA1c explains a good proportion of the heterogeneity in observed 1-year changes in HbA1c. Again, we recognise that the inclusion of a random-effects term attenuates differences between models, and note that there was a conspicuous difference in DIC between the unadjusted and unadjusted models in fixed-effects analyses (180.44 versus 30.37).

Again, we concluded that the health economic model should use the adjusted baseline synthesis model to estimate 1-year change in HbA1c. To give a worked example, an individual with a sampled baseline HbA1c of 8% who received metformin-pioglitazone-sulfonylurea (which is estimated, in the relevant NMA to result in HbA1c 1.45% higher at 1 year than in people taking insulin glargine-metformin) would have their 1-year HbA1c estimated as follows:

$$H_{1,i} = 8 - 0.12 - 0.98(8 - 7.5) + 1.45$$

$$= 8.84$$

We note that the median estimates of the 1-year change and the adjustment for baseline coefficient are small and close to 1, respectively; this means that, when evaluated at the central estimate, the 1-year estimate of HbA1c on insulin glargine-metformin will be 'concertinaed' to a relatively narrow range of values close to the centring point of 7.5 regardless of sampled starting HbA1c, which reduces inter-patient heterogeneity. However, inter-treatment differences are unaffected, and this will only rarely be the case when these coefficients are sampled from their full distributions in the probabilistic analysis on which our base case relies.

3.5.2 Treatment dropouts due to intolerance

Relative effectiveness evidence for treatment dropouts due to intolerance was dichotomous in nature, and was synthesised using a binomial-likelihood–cloglog-link model (see section 3.6.2 of the main guideline). An identical approach was taken for the baseline synthesis model. This means that the annual rate of events with each treatment is estimated simply on a logarithmic scale as:

$$r_i = r_1 + d_{1i} \quad \textbf{(3)}$$

, where r_i is the log-rate (per year) of events with treatment i and d_{1i} is the log-hazard ratio for treatment i compared with treatment 1, which is derived from the NMA.

3.5.2.1 Initial therapy

For initial therapy, the reference option in the network was metformin. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.1.3), 47 studies reported rate of treatment dropout due to intolerance on metformin. Because the fixed-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model without a random-effects term.

Model outputs are shown in table 33.

Table 33: Baseline synthesis model: treatment dropout due to intolerance – metformin as initial therapy

		Median (95%CrI)
1-year log event rate with metformin	predicted	n/a (fixed-effects model)
	mean	-2.935 (-3.102, -2.777)
tau		n/a (fixed-effects model)
DIC		256.24

To give a worked example, the cohort receiving pioglitazone (which is associated with a log-hazard ratio of 0.475 compared with people taking metformin) has its log-dropout-rate estimated as follows:

$$r_i = -2.935 + 0.475$$

$$= -2.460$$

, which, when transformed to the natural scale, equates to a rate of 0.085 dropouts per year.

3.5.2.2 First intensification

The reference option in the first intensification network was metformin-sulfonylurea. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.2.3), 22 studies reported rate of dropout due to adverse events on metformin-sulfonylurea at 1 year. Because the random-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model with a random-effects term. It was given a noninformative U(0,5) prior.

Model outputs are shown in Table 34.

Table 34: Baseline synthesis model: treatment dropout due to intolerance – metformin-sulfonylurea at first intensification

		Median (95%CrI)
1-year log event rate with metformin-sulfonylurea	predicted	-3.168 (-4.335, -2.012)
	mean	-3.165 (-3.463, -2.872)
tau		0.530 (0.328, 0.864)
DIC		124.20

To give a worked example, the cohort receiving liraglutide-metformin (which is associated with a log-hazard ratio of 1.362 compared with people taking metformin-sulfonylurea) has its log-dropout-rate estimated as follows:

$$r_i = -3.165 + 1.362$$

$$= -1.803$$

, which, when transformed to the natural scale, equates to a rate of 0.165 dropouts per year.

3.5.2.3 Second intensification

The reference option in the second intensification network was metformin-NPH insulin. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.3.3), 5 studies reported rate of dropout due to intolerance on metformin-NPH insulin at 1 year. Because the fixed-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model without a random-effects term.

Model outputs are shown in table 35.

Table 35: Baseline synthesis model: dropout due to intolerance – metformin-NPH insulin at second intensification

		Median (95%CrI)
1-year log event rate with metformin-NPH insulin	predicted	n/a (fixed-effects model)
	mean	-2.613 (-3.247, -2.090)
tau		n/a (fixed-effects model)
DIC		124.20

To give a worked example, the cohort receiving metformin-pioglitazone-sulfonylurea (which is associated with a log-hazard ratio of −1.322 compared with people taking metformin-NPH insulin) has its log-dropout-rate estimated as follows:

$$r_i = -2.613 - 1.322$$

$$= -3.935$$

, which, when transformed to the natural scale, equates to a rate of 0.019 dropouts per year.

3.5.3 Weight

Weight is another continuous variable that is estimated on a natural scale as per equation **(1)**. We explored baseline weight and baseline HbA1c as potential covariates of outcome; the adjusted analyses did not result in better-fitting models, so are not reported here.

3.5.3.1 Initial therapy

For initial therapy, the reference option in the network was metformin. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.1.5), 4 studies reported change in weight on metformin at 1 year. Because the random-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model with a random-effects term. It was given a noninformative U(0,5) prior.

Model outputs are shown in table 36.

Table 36: Baseline synthesis model: change in weight (kg) at 1 year – metformin as initial therapy

		Median (95%CrI)
1-year change with metformin	predicted	-2.058 (-4.919, 0.417)
	mean	-2.066 (-3.560, -0.869)
tau		0.451 (0.020, 3.252)
DIC		9.485

The model estimates that, on average, people lose around 2 kg after a year's treatment with metformin.

3.5.3.2 First intensification

The reference option in the first intensification network was metformin-sulfonylurea. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.2.5), 6 studies reported change in weight on metformin-sulfonylurea at 1 year. Because the fixed-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model without a random-effects term.

Model outputs are shown in table 37.

Table 37: Baseline synthesis model: change in weight (kg) at 1 year – metformin-sulfonylurea at first intensification

		Median (95%CrI)
1-year change with metformin-sulfonylurea	predicted	n/a (fixed-effects model)
	mean	1.354 (1.169, 1.542)
Tau		n/a (fixed-effects model)
DIC		14.943

The model estimates that, on average, people gain over 1 kg during their first year's treatment with metformin-sulfonylurea.

3.5.3.3 Second intensification

The reference option in the network was metformin-NPH insulin. In the evidence assembled for the NMA (see Appendix J of the main guideline, section J.1.3.5), 4 studies reported change in weight at up to 1 year with metformin-NPH insulin. Because the fixed-effects NMA was selected as having a better fit to the data, we ran the baseline synthesis model without a random-effects term.

Model outputs are shown in table 38.

Table 38: Baseline synthesis model: change in weight (kg) at up to 1 year – metformin-NPH insulin at second intensification

		Median (95%CrI)
1-year change with metformin-NPH insulin	predicted	n/a (fixed-effects model)
	mean	1.703 (1.201, 2.210)
tau		n/a (fixed-effects model)
DIC		14.954

The model estimates that, on average, people gain more than 1.7 kg during their first year's treatment with metformin-NPH insulin.

3.5.4 Hypoglycaemia rates

In addition to the baseline data required for UKPDS OM1, baseline hypoglycaemia rates were required for each therapy level, to which the relativities for each treatment from the NMA were applied.

The population of people with type 2 diabetes is heterogeneous and in the population, hypoglycaemia rates are not well researched (Zammitt and Frier 2005). Hypoglycaemia rates will vary according to individual factors such as type 2 diabetes duration and length of time on a particular therapy; reported hypoglycaemia rates may be skewed as many people will not experience any hypoglycaemic events (Amiel et al. 2008).

Baseline hypoglycaemia rates could have been taken from the included RCT evidence. However, the GDG felt that differences in hypoglycaemia definitions, data collection, data recording and reporting could mean RCT data were not reflective of clinical reality. Also, the extra scrutiny arising from being part of a trial may have led to higher reported rates.

Instead, the GDG preferred to use baseline hypoglycaemia rates from epidemiological studies. Ideally, baseline hypoglycaemia rates would be taken from studies that were:

- prospective, UK based studies
- representative of the populations being modelled
- clear clinical definitions of hypoglycaemia with which the GDG agreed
- covered all severities of hypoglycaemic episodes and
- gave clear descriptions of the treatment
- s people were taking.

As already highlighted in the main guideline (see section 3.2.4.1 of the main guideline), RCTs measure and report hypoglycaemic episodes in a variety of ways. As well as using a variety of sometimes undefined categories, some RCTs only reported those hypoglycaemic episodes that result in attendance at, or use of, NHS services.

In order to establish to which treatment within the NMA any baseline hypoglycaemia rate should be applied, it was necessary to have clear information on the treatments people in the study were taking.

3.5.4.1 Second intensification

Only 1 prospective UK study was found (Donnelly et al. 2005). This 1-month study of insulin-treated Scottish people with diabetes gave self-reported rates of all hypoglycaemic episodes, stratified by treatment and for people with type 1 and type 2 diabetes separately. People were randomly selected from an existing community database of people with diabetes. 53% of the people with type 2 diabetes were male with a mean age of 65 years, mean diabetes duration of 14 years and mean HbA1c of 8.9%. These people have slightly longer diabetes duration and higher HbA1c than the second intensification population modelled here (see

table 20). However, this was the only study found that was a UK prospective study, clearly reported all levels of hypoglycaemic episodes and differentiated rates by the treatments being taken. These study qualities were felt to outweigh any potential benefit of finding a better matching population in a retrospective study, or of a study that only reported some hypoglycaemic episodes.

Donnelly et al. (2005) reported 236 hypoglycaemic episodes in the 173 people with type 2 diabetes during the study, of which 5 episodes in 5 people were classed as severe (2% of all episodes). This gave a rate of 1.36 all hypoglycaemic episodes per person during the month of the study. Whilst the paper usefully reported hypoglycaemia rates by insulin type, it did not report specific insulin brands. Also, they were not clear on which non-insulin medications people were taking. The largest group of people (120, 70%) were reported as being on "biphasic insulin". For this group, a rate of 1.22 hypoglycaemic episodes (all severities) per person month was reported (see table 40, equivalent to 14.6 hypoglycaemic episodes per person per year or slightly more than 1 per month).

As the treatment comparisons within the second intensification NMA were brand-specific, an assumption was necessary as to which biphasic insulin people were most likely to be taking. The GDG felt the most likely treatment option in this study population would be NPH insulin mix 70/30-metformin. Whilst NPH insulin mix 70/30-metformin did not have the minimum dataset to allow it to be included in the health economic model (see 3.4), it was in the hypoglycaemia NMA and therefore the baseline hypoglycaemia rate could be applied to NPH insulin mix 70/30-metformin.

Given that the relative effects on hypoglycaemia rates were applied from the NMA, the choice of treatment to which the baseline hypoglycaemia rates were applied would not have impacted the treatment rankings produced by the original health economic model. However, it may have affected the absolute levels of hypoglycaemic episodes which in turn, via the costs and utilities applied, may have influenced the overall impact of hypoglycaemia (as opposed to HbA1c or treatment-related weight-change) on the cost-effectiveness results. The impact of using lower or higher baseline hypoglycaemia rates was tested in sensitivity analyses (see 3.11.2.4).

A number of alternative UK papers to Donnelly et al. (2005) were considered as sources for the rates of hypoglycaemia rates (Henderson et al. 2003; Leese et al. 2003; UK Hypoglycaemia Study Group 2007; Wright et al. 2006), but Donnelly et al. (2005) was considered to be the highest quality and most relevant of the papers (see table 39). Two systematic reviews highlighted no other UK based papers to be considered (Amiel et al. 2008; Zammitt and Frier 2005).

Table 39: Papers considered as alternative sources of baseline hypoglycaemia rates for second intensification

Reference	Comments
Henderson et al. 2003	Retrospective study of Scottish people taking insulin at least twice daily. Hypoglycaemic episodes reported in categories, rather than numbers of events. Results did not differentiate by insulin type and concomitant oral medications not listed. Rate of severe hypoglycaemic episodes consistent with Donnelly et al. (2005)
Leese et al. 2003	Retrospective Scottish study from same database as Donnelly et al. (2005). Insulin type not specified, but used here for initial therapy rates
UK Hypoglycaemia Study Group 2007	Prospective multicentre UK study with high proportion of males in cohort (70% of people with type 2 diabetes). Did not specify insulin type or concomitant oral medications
Wright et al. 2006	UKPDS RCT based analysis that reported by hypoglycaemia rates by therapy. Only reported proportion of people and their most severe hypoglycaemic event in previous 4 months, not numbers of events

3.5.4.2 Initial therapy

No prospective UK studies providing rates of all hypoglycaemic episodes were found for initial therapy or first intensification.

Leese et al. (2003) reported only severe hypoglycaemia rates in people with type 2 diabetes. The authors used the same UK community database of people with type 2 diabetes as Donnelly et al. (2005) and NHS activity records to retrospectively identify people with severe hypoglycaemic episodes that were treated by the NHS. 91 people were identified who had 132 episodes over 1 year and results were reported by overall treatment groups. These people had a mean age of 66 and a mean diabetes duration of 8 years, so were comparable to the second intensification population modelled here (see table 20).

Leese et al. (2003) reported an incidence of 0.9 severe hypoglycaemic episodes per 100 person years, for people taking sulfonylureas. It was assumed these people were taking sulfonylurea alone i.e. as initial therapy (see table 2 in the paper (Leese et al. 2003)).

In order to calculate the baseline rate of all hypoglycaemic episodes for initial therapy, 2 assumptions were necessary. Firstly, as Leese et al. (2003) only reported severe hypoglycaemic episodes that required NHS treatment, the proportion of severe hypoglycaemic episodes that required NHS treatment was taken to be 53% of episodes (Hammer et al. 2009). This is the same proportion as used here in the costing of severe hypoglycaemic episodes and the GDG were happy to use this proportion (see 3.9.4). Secondly, from the data reported in Donnelly et al. (2005) severe hypoglycaemic episodes were assumed to represent 2% of all hypoglycaemic episodes (5 out of 236 events).

Applying these assumptions to the rate in Leese et al. (2003) resulted in a baseline initial therapy rate for all hypoglycaemic episodes of 0.8 events per person per year for people on sulfonylurea (see table 40).

3.5.4.3 First Intensification

For first intensification, Bodmer et al. (2008) reported adjusted odds ratios of hypoglycaemic episodes for people with type 2 diabetes taking various treatment options. The authors used UK General Practice Research Database (GPRD) data to retrospectively analyse UK people with type 2 diabetes over 10 years who were and were not recorded by their general practice as experiencing hypoglycaemia (Bodmer et al. 2008). The authors selected over 9000 people (2000 cases and 7300 matched controls) who had a mean age of 61 years and of whom 45% were male. Bodmer et al. (2008) calculated odds ratios for hypoglycaemic episodes, adjusted for metformin, sulfonylurea and insulin use and combinations of those 3 drugs. The adjusted odds ratios (compared with non-use of the givne given drug(s)) for sulfonylurea use and metformin with sulfonylurea use were 2.79 and 4.04 respectively. The sulfonylurea hypoglycaemia rate from Leese et al (2003) was converted to odds, multiplied by the ratio between the two odds ratios from Bodmer et al (2008) and converted back to a rate to produce an annual rate per person of 1.01 episodes of all of for people taking metformin-sulfonylurea (see table 40).

Bodmer et al. (2008) did not report useable hypoglycaemia rates by specific treatment. The hypoglycaemia definition employed by Bodmer et al. (2008) required hypoglycaemia to have been reported to the person's GP. Such episodes may have been severe (requiring external assistance) but may also have included episodic hypoglycaemia reported by the person at a consultation. It was assumed that the adjusted odds ratios could be applied to the all hypoglycaemic episode rates calculated for initial therapy.

The GDG reviewed and were happy with the baseline annual rates of all hypoglycaemic episodes for each therapy level (see table 40). Baseline hypoglycaemia rates for each therapy were tested in sensitivity analyses (see 3.11.2.4).

Table 40: Estimated baseline rates of all hypoglycaemic episodes by therapy level

Therapy Level	Treatment	Annual Rate of All Hypoglycaemic Episodes	Source
Initial Therapy	Sulfonylurea	0.79	Leese et al. (2003)
First Intensification	Metformin-Sulfonylurea	1.01	Bodmer et al. (2008)
Second Intensification	NPH mix 70/30-Metformin	14.6	Donnelly et al. (2005)

3.5.4.4 Extraction of Hypoglycaemia Data from Included RCTs

The GDG were most interested in rates of all hypoglycaemic episodes. However, not all of the included clinical studies reported all hypoglycaemic episodes and this would have been a severely limiting factor in the number of comparators that could be modelled in the original health economic model.

Table 41: GDG hierarchy of RCT reported hypoglycaemic episodes

Category (in descending priority order)
All hypoglycaemic events (number of events)
All hypoglycaemic events (number of people)
Symptomatic hypoglycaemia
Symptomatic (confirmed) hypoglycaemia
Symptomatic (unconfirmed) hypoglycaemia
Confirmed hypoglycaemia
Minor hypoglycaemic events
Minor (confirmed) hypoglycaemia
Minor (unconfirmed) hypoglycaemia
Moderate hypoglycaemia
Moderate/severe hypoglycaemia
Major/severe hypoglycaemic event
Nocturnal hypoglycaemia
Nocturnal (symptomatic) hypoglycaemia
Nocturnal (confirmed) hypoglycaemia
Nocturnal (mild) hypoglycaemia

The commonest hypoglycaemia categories reported in the included clinical papers were all hypoglycaemic events (number of people) and major/severe hypoglycaemic episodes. However, the majority of papers reported 0 major/severe hypoglycaemic episodes in at least 1 arm, which caused technical issues for the NMA. It was not felt to be useful to add a 0.5 continuity correction to the data for comparison of rates so for papers reporting 0 events either a different hypoglycaemia category was used, or the paper was not able to be included in the NMA.

To increase the number of comparisons that could be modelled, a hierarchical approach was taken to the hypoglycaemia NMA. The GDG prioritised hypoglycaemia categories within a list of categories compiled from the included RCTs (see table 41). Papers reporting any of the categories were therefore in the NMA. Where a paper reported more than 1 hypoglycaemia category, data from the category higher in the hierarchy GDG were used. In addition, data reporting number of events were prioritised over data reporting number of people experiencing events. There was greater reliance on lower hierarchy levels at second intensification than at initial therapy or first intensification; this is likely to be a by-product of greater focus at second intensification on hypoglycaemia outcomes (see table 42).

Table 42: Highest level of hypoglycaemic episodes reported

Included papers reporting:	Initial therapy	First intensification	Second intensification
All hypoglycaemic events (events or people)	44	20	21
Symptomatic hypoglycaemia	14	5	9
Confirmed, minor, moderate or major hypoglycaemia	5	3	8

Table 43: Papers included in hypoglycaemia rate validation exercise

Treatment Level	Papers Reporting Non-Zero All or Symptomatic Hypoglycaemia Events In At Least 1 Arm
Initial Therapy	Jain et al. (2006)
	Jovanovic et al. (2000)
First Intensification	Gallwitz et al. (2012)
	Goke et al. (2010)
	Nauck et al. (2007)
	Ristic et al. (2006)
Second Intensification	Fritsche et al. (2003)
	Goudswaard et al. (2004)
	Janka et al. (2005)
	Kilo et al. (2003)
	Kvapil et al. (2006)
	Pan et al. (2007)
	Raz et al. (2005)
	Ushakova et al. (2007)
	Yki-Jarvinen et al. (1999)

It can be seen in figure 12 this assumption holds somewhat stronger for initial therapy and first intensification than it does for second intensification. However, the 2 outliers on the second intensification paper were justifiably different to other papers. Janka et al. (2005, the lowest point on the y-axis) reported a greater number of symptomatic hypoglycaemic episodes than all hypoglycaemic episodes – the more believable all episodes number was used in the NMA. Goudswaard et al. (2004) reported confirmed rather than symptomatic hypoglycaemic episodes, which may explain what appears to be a lower than expected rate shown.

Despite the issues highlighted, using this comparability assumption and hierarchical data selection was felt to be more useful than modelling fewer comparators that only reported the all hypoglycaemic events category.

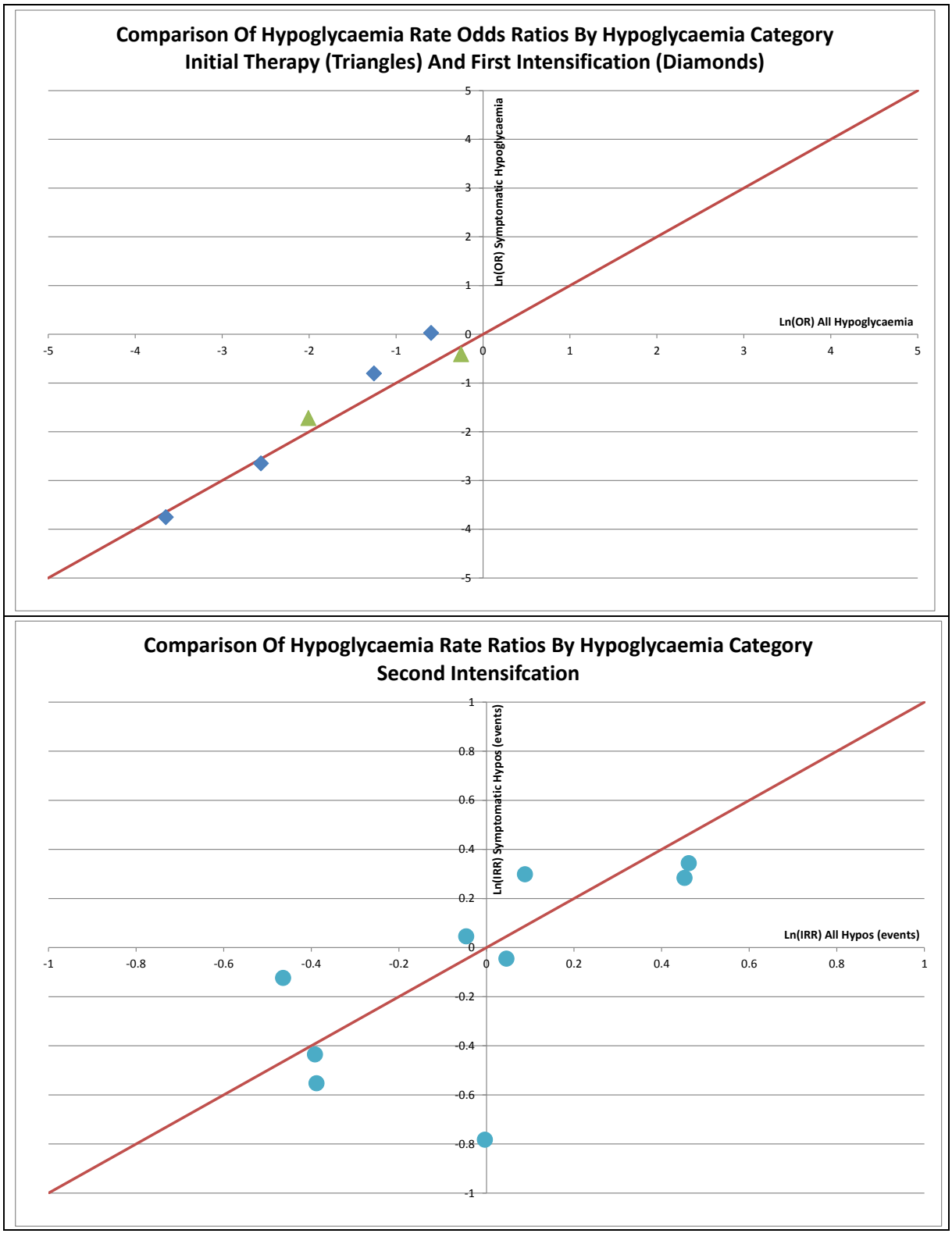


Figure 12: Comparison of Hypoglycaemia Rates Within RCTs by Therapy Level

3.6 Summary of treatment effect data

We incorporated the baseline models and relative effect (NMA) models into the original health economic model by capturing the sample-by-sample output (CODA) of the relevant posterior distributions as estimated in WinBUGS. We used these data to calculate summary statistics and, critically, to capture the correlations between parameters. To implement the effects, the original health economic model sampled from multivariate normal distributions parameterised using means, standard deviations and correlations from these data. For each phase of therapy, all 4 effects were combined into a single multivariate matrix; this theoretically allowed correlations between different effects to be specified though, in the base case, all effects were assumed to be independent (that is, all sectors of the matrix that specified the correlations between parameters from separate analyses were set to 0).

Means, standard deviations and correlation matrices for all effects are shown in tables 44–47 (initial therapy), 48–51 (first intensification) and 52–55 (second intensification). These tables cover all treatments included in the NMAs, rather than only those for which the minimum dataset (see 3.4) was available.

Table 44: Safety and efficacy data inputs for health economic model – initial therapy – HbA1c at 1 year

			Absolute change (%)			Relative effect (%)							
			Metformin			Acarbose	Pioglitazone	Placebo	Repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (MR)	Vildagliptin
			Mean	Pred	Beta								
Mean			-0.789	-0.787	-0.499	0.420	0.039	0.839	-0.045	0.163	0.153	0.086	0.457
SD			0.252	0.444	0.154	0.288	0.121	0.248	0.211	0.153	0.112	0.474	0.165
			Correlation matrix										
Absolute change (%)	Metformin	Mean	1.000	-	-	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-	-	-
		Beta	-0.798	-0.499	1.000	-	-	-	-	-	-	-	-
Relative effect (%)	Acarbose		-	-	-	1.000	-	-	-	-	-	-	-
	Pioglitazone		-	-	-	0.140	1.000	-	-	-	-	-	-
	Placebo		-	-	-	0.860	0.146	1.000	-	-	-	-	-
	Repaglinide		-	-	-	0.140	0.299	0.166	1.000	-	-	-	-
	Sitagliptin		-	-	-	0.105	0.186	0.114	0.187	1.000	-	-	-
	Sulfonylurea		-	-	-	0.260	0.540	0.299	0.534	0.347	1.000	-	-
	Sulfonylurea (MR)		-	-	-	0.018	0.097	0.021	0.030	0.005	0.052	1.000	-
	Vildagliptin		-	-	-	0.467	0.222	0.540	0.204	0.146	0.386	0.016	1.000

Table 45: Safety and efficacy data inputs for health economic model – initial therapy – weight at 1 year

			Absolute change (kg)		Relative effect (kg)						
			Metformin		Pioglitazone	Placebo	Repaglinide	Sitagliptin	Sulfonylurea	Sulfonylurea (MR)	Vildagliptin
			Mean	Pred							
Mean			-2.101	-2.104	3.458	2.492	3.192	1.838	3.592	7.277	2.196
SD			0.638	1.258	2.079	3.066	2.051	2.692	1.540	6.140	2.173
Correlation matrix											
Absolute change (kg)	Metformin	Mean	1.000	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-
Relative effect (kg)	Pioglitazone		-	-	1.000	-	-	-	-	-	-
	Placebo		-	-	-0.006	1.000	-	-	-	-	-
	Repaglinide		-	-	0.517	-0.013	1.000	-	-	-	-
	Sitagliptin		-	-	0.408	0.005	0.457	1.000	-	-	-
	Sulfonylurea		-	-	0.681	-0.012	0.760	0.591	1.000	-	-
	Sulfonylurea (MR)		-	-	0.159	0.003	0.092	0.073	0.123	1.000	-
	Vildagliptin		-	-	-0.007	0.700	-0.009	0.011	-0.015	-0.000	1.000

Table 46: Safety and efficacy data inputs for health economic model – initial therapy – incidence of hypoglycaemia (annual rate)

			Baseline ln(rate)		Relative effect – ln(HR)									
			Placebo		Acarbose	Linagliptin	Metformin	Pioglitazone	Repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Sulfonylurea (MR)	Vildagliptin
			Mean	Pred										
Mean			-3.016	-3.017	0.630	-0.561	0.407	0.442	1.653	1.085	0.215	1.818	1.162	0.123
SD			0.287	1.148	0.541	0.821	0.231	0.281	0.371	0.983	0.263	0.219	0.609	0.369
Correlation matrix														
Baseline ln(rate)	Placebo	Mean	1.000	-	-	-	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-	-	-	-
Relative effect – ln(HR)	Acarbose		-	-	1.000	-	-	-	-	-	-	-	-	-
	Linagliptin		-	-	0.039	1.000	-	-	-	-	-	-	-	-
	Metformin		-	-	0.224	0.154	1.000	-	-	-	-	-	-	-
	Pioglitazone		-	-	0.155	0.074	0.350	1.000	-	-	-	-	-	-
	Repaglinide		-	-	-0.002	0.005	0.057	0.047	1.000	-	-	-	-	-
	Saxagliptin		-	-	0.005	0.006	0.011	0.017	0.002	1.000	-	-	-	-
	Sitagliptin		-	-	0.193	0.087	0.487	0.288	0.025	-0.005	1.000	-	-	-
	Sulfonylurea		-	-	0.338	0.110	0.644	0.553	0.037	0.005	0.523	1.000	-	-
	Sulfonylurea (MR)		-	-	0.114	0.032	0.215	0.200	0.027	0.011	0.168	0.330	1.000	-
	Vildagliptin		-	-	0.057	0.047	0.199	0.076	0.001	0.020	0.115	0.130	0.038	1.000

Table 47: Safety and efficacy data inputs for health economic model – initial therapy – dropouts due to adverse events (annual rate)

			Baseline ln(rate)		Relative effect – ln(HR)									
			Placebo		Acarbose	Linagliptin	Metformin	Metformin (MR)	Pioglitazone	Repaglinide	Saxagliptin	Sitagliptin	Sulfonylurea	Vildagliptin
			Mean	Pred										
Mean			-2.795	n/a	0.809	-0.220	0.377	1.032	0.475	-0.443	0.011	0.041	0.545	-0.015
SD			0.149	-	0.189	0.442	0.140	0.666	0.172	0.317	0.887	0.181	0.153	0.186
Correlation matrix														
Baseline ln(rate)	Placebo	Mean	1.000	-	-	-	-	-	-	-	-	-	-	-
		Pred	-	-	-	-	-	-	-	-	-	-	-	-
Relative effect – ln(HR)	Acarbose		-	-	1.000	-	-	-	-	-	-	-	-	-
	Linagliptin		-	-	0.029	1.000	-	-	-	-	-	-	-	-
	Metformin		-	-	0.215	0.148	1.000	-	-	-	-	-	-	-
	Metformin (MR)		-	-	0.005	0.018	0.020	1.000	-	-	-	-	-	-
	Pioglitazone		-	-	0.156	0.108	0.643	0.016	1.000	-	-	-	-	-
	Repaglinide		-	-	0.004	-0.002	0.039	-0.000	0.041	1.000	-	-	-	-
	Saxagliptin		-	-	0.016	-0.009	0.014	-0.022	0.008	0.013	1.000	-	-	-
	Sitagliptin		-	-	0.108	0.085	0.472	0.020	0.335	0.042	0.010	1.000	-	-
	Sulfonylurea		-	-	0.179	0.126	0.825	0.019	0.656	0.047	0.016	0.453	1.000	-
	Vildagliptin		-	-	0.215	0.060	0.336	0.001	0.268	0.010	0.013	0.174	0.282	1.000

Table 48: Safety and efficacy data inputs for health economic model – first intensification – HbA1c at 1 year

			Absolute change (%)			Relative effect (%)									
			Metformin-sulfonylurea			Exenatide-metformin	Linagliptin-metformin	Liraglutide-metformin	Metformin-nateglinide	Metformin-pioglitazone	Metformin-saxagliptin	Metformin-sitagliptin	Metformin-vildagliptin	Pioglitazone-sitagliptin	Pioglitazone-sulfonylurea
			Mean	Pred	Beta										
Mean			-0.665	-0.658	-0.469	0.199	0.103	-0.144	-0.235	-0.039	0.062	0.204	0.036	-0.043	0.159
SD			0.138	0.377	0.185	0.346	0.322	0.236	0.203	0.210	0.325	0.254	0.201	0.401	0.328
			Correlation matrix												
Absolute change (%)	Metformin-sulfonylurea	Mean	1.000	-	-	-	-	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-	-	-	-	-
		Beta	-0.681	-0.244	1.000	-	-	-	-	-	-	-	-	-	-
Relative effect (%)	Exenatide-metformin		-	-	-	1.000	-	-	-	-	-	-	-	-	-
	Linagliptin-metformin		-	-	-	0.019	1.000	-	-	-	-	-	-	-	-
	Liraglutide-metformin		-	-	-	-0.014	0.005	1.000	-	-	-	-	-	-	-
	Metformin-nateglinide		-	-	-	0.017	0.006	-0.005	1.000	-	-	-	-	-	-
	Metformin-pioglitazone		-	-	-	0.016	-0.005	0.021	-0.009	1.000	-	-	-	-	-
	Metformin-saxagliptin		-	-	-	-0.009	0.005	0.022	-0.013	-0.007	1.000	-	-	-	-
	Metformin-sitagliptin		-	-	-	-0.010	0.020	0.532	-0.010	-0.006	0.025	1.000	-	-	-
	Metformin-vildagliptin		-	-	-	0.010	-0.005	0.011	-0.012	0.354	-0.000	0.006	1.000	-	-
	Pioglitazone-sitagliptin		-	-	-	0.014	0.005	0.044	-0.003	0.520	-0.025	0.030	0.186	1.000	-
	Pioglitazone-sulfonylurea		-	-	-	0.012	-0.010	0.018	-0.012	0.009	-0.008	0.012	0.008	0.002	1.000

Table 49: Safety and efficacy data inputs for health economic model – first intensification – weight at 1 year

			Absolute change (kg)		Relative effect (kg)						
			Metformin-sulfonylurea		Exenatide-metformin	Linagliptin-metformin	Liraglutide-metformin	Metformin-pioglitazone	Metformin-sitagliptin	Metformin-vildagliptin	Pioglitazone-sitagliptin
			Mean	Pred							
Mean			1.354	n/a	-4.202	-2.600	-4.444	0.552	-2.482	-1.796	1.772
SD			0.095	-	1.663	0.318	0.501	0.389	0.378	0.165	1.086
Correlation matrix											
Absolute change (kg)	Metformin-sulfonylurea	Mean	1.000	-	-	-	-	-	-	-	-
		Pred	-	-	-	-	-	-	-	-	-
Relative effect (kg)	Exenatide-metformin		-	-	1.000	-	-	-	-	-	-
	Linagliptin-metformin		-	-	0.002	1.000	-	-	-	-	-
	Liraglutide-metformin		-	-	-0.015	-0.001	1.000	-	-	-	-
	Metformin-pioglitazone		-	-	-0.001	-0.008	-0.005	1.000	-	-	-
	Metformin-sitagliptin		-	-	-0.005	-0.004	0.684	-0.015	1.000	-	-
	Metformin-vildagliptin		-	-	0.018	-0.004	-0.005	0.441	-0.012	1.000	-
	Pioglitazone-sitagliptin		-	-	0.004	0.010	0.004	0.344	0.007	0.146	1.000

Table 50: Safety and efficacy data inputs for health economic model – first intensification – incidence of hypoglycaemia (annual rate)

			Baseline ln(rate)		Relative effect – ln(HR)											
			Met-SU		Acarbose-met	Exenatide (1-wkly)-met	Exenatide-met	Linagliptin-met	Liraglutide-met	Lixisenatide-met	Met-nateglinide	Met-pio	Met-saxagliptin	Met-sitagliptin	Met-vildagliptin	Pio-SU
			Mean	Pred												
Mean			-0.689	-0.701	-4.006	-3.187	-1.246	-2.213	-1.637	-3.108	-0.708	-2.753	-3.675	-2.049	-1.126	-0.363
SD			0.462	1.955	2.427	1.113	0.732	0.675	0.411	1.102	0.531	0.519	0.730	0.420	0.646	0.745
			Correlation matrix													
Baseline ln(rate)	Met-SU	Mean	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-
Relative effect – ln(HR)	Acarbose-met		-	-	1.000	-	-	-	-	-	-	-	-	-	-	-
	Exenatide (once wkly)-Met		-	-	-0.008	1.000	-	-	-	-	-	-	-	-	-	-
	Exenatide-met			-	0.001	-0.008	1.000	-	-	-	-	-	-	-	-	-
	Linagliptin-met		-	-	0.009	-0.024	-0.024	1.000	-	-	-	-	-	-	-	-
	Liraglutide-met		-	-	0.018	0.083	-0.012	-0.002	1.000	-	-	-	-	-	-	-
	Lixisenatide-met		-	-	-0.002	0.000	0.660	-0.022	-0.005	1.000	-	-	-	-	-	-
	Met-nateglinide		-	-	0.003	-0.024	-0.002	0.014	-0.010	-0.005	1.000	-	-	-	-	-
	Met-pio		-	-	0.004	0.187	-0.009	0.000	0.076	0.006	0.013	1.000	-	-	-	-
	Met-saxagliptin		-	-	0.003	-0.014	0.013	0.006	-0.004	-0.001	-0.016	-0.015	1.000	-	-	-
	Met-sitagliptin		-	-	0.007	0.273	-0.013	-0.016	0.349	-0.003	-0.010	0.163	-0.011	1.000	-	-
	Met-vildagliptin		-	-	0.013	0.022	-0.010	0.001	0.014	-0.015	-0.004	0.103	-0.010	0.042	1.000	-
	Pio-SU		-	-	-0.007	-0.006	-0.003	-0.003	-0.000	-0.014	-0.007	0.013	-0.001	0.022	-0.008	1.000

Met: metformin; pio: pioglitazone; SU: sulfonylurea

Table 51: Safety and efficacy data inputs for health economic model – first intensification – dropouts due to AEs (annual rate)

			Baseline ln(rate)		Relative effect – ln(HR)												
			Met-SU		Acarbose-Met	Exen (1-wkly)-Met	Exen-Met	Lina-Met	Liraglutide-Met	Lixisenatide-Met	Met-nateglinide	Met-Pio	Met-Saxa	Met-Sita	Met-Vilda	Pio-Sita	Pio-SU	Sita-SU
			Mean	Pred														
Mean			-3.163	-3.174	-2.071	1.084	0.750	-0.186	1.362	0.503	-0.223	0.308	-0.117	0.322	0.133	-0.301	-0.217	0.906
SD			0.149	0.573	2.403	0.717	0.527	0.484	0.385	0.822	0.578	0.335	0.625	0.370	0.366	0.935	0.630	1.132
Correlation matrix																		
Baselin ln(rate)	Met-SU	Mean	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Relative effect – ln(HR)	Acarbose-Met			-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-
	Exenatide (1-wkly)-Met			-	-0.011	1.000	-	-	-	-	-	-	-	-	-	-	-	-
	Exenatide-met		-	-	0.015	0.017	1.000	-	-	-	-	-	-	-	-	-	-	-
	Lina-met		-	-	0.003	0.005	-0.007	1.000	-	-	-	-	-	-	-	-	-	-
	Liraglutide-met		-	-	0.009	0.087	0.006	0.008	1.000	-	-	-	-	-	-	-	-	-
	Lixisenatide-met		-	-	0.001	0.007	0.649	0.009	0.001	1.000	-	-	-	-	-	-	-	-
	Met-nateglinide		-	-	-0.009	-0.014	0.004	-0.016	0.003	0.000	1.000	-	-	-	-	-	-	-
	Met-pio		-	-	0.007	0.281	0.010	0.017	0.051	0.012	-0.011	1.000	-	-	-	-	-	-
	Met-saxa		-	-	0.002	0.013	0.007	0.007	0.005	0.011	-0.019	-0.002	1.000	-	-	-	-	-
	Met-sita		-	-	0.006	0.279	-0.004	0.013	0.316	-0.008	0.005	0.172	0.004	1.000	-	-	-	-
	Met-vilda		-	-	-0.005	0.067	-0.015	0.020	0.011	-0.012	-0.030	0.188	0.000	0.022	1.000	-	-	-
	Pio-sita		-	-	0.010	0.104	0.003	0.010	0.024	0.017	0.003	0.355	0.013	0.061	0.090	1.000	-	-
	Pio-SU		-	-	0.022	-0.003	-0.012	-0.016	0.006	-0.001	0.006	0.003	-0.016	0.019	0.007	0.007	1.000	-
	Sita-SU		-	-	0.000	0.014	-0.010	0.021	0.007	-0.014	-0.015	0.001	-0.001	0.013	0.004	0.017	-0.004	1.000

Exen:exenatide; Lina: linagliptin; Met: metformin; pio: pioglitazone; SU: sulfonylurea; sita: sitagliptin; vilda: vildagliptin

Table 52: Safety and efficacy data inputs for health economic model – second intensification – HbA1c at 1 year

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Mean	-0.15	-0.14	-0.95	1.95	1.05	-0.54	-0.71	-0.27	-1.24	-0.51	-0.18	0.07	-0.53	-0.08	0.13	0.25	-0.33	0.30	-0.33	-0.40	-0.04	0.64	-0.57	-0.39	-0.41	-1.65	1.05	1.45	2.25	1.69	-0.01	0.65	0.41	0.48	0.47
SD	0.45	0.63	0.44	0.96	1.05	0.52	0.44	0.47	0.66	0.57	0.43	0.45	0.46	0.34	0.32	0.35	0.32	0.34	0.58	0.35	0.28	1.05	0.48	0.30	0.49	0.59	0.84	0.90	1.03	0.97	0.33	0.70	0.75	0.43	0.35
	Correlation matrix																																		
1	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-0.93	-	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	0.91	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	0.10	0.08	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	0.12	0.10	0.83	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	-	0.12	0.11	0.58	0.70	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	-	0.08	0.07	0.81	0.67	0.46	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	-	0.10	0.08	0.64	0.77	0.54	0.51	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	0.13	0.12	0.58	0.69	0.83	0.46	0.53	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-	0.14	0.12	0.29	0.35	0.30	0.23	0.26	0.33	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	0.13	0.11	0.29	0.35	0.30	0.24	0.26	0.32	0.60	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	0.01	-0.00	-0.02	-0.02	-0.01	-0.03	-0.00	-0.01	0.01	-0.00	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-0.00	-0.00	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.00	-0.01	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-0.03	-0.03	0.01	0.02	0.01	0.00	0.02	0.01	0.01	0.02	0.00	0.00	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	0.18	0.17	0.42	0.50	0.55	0.33	0.37	0.64	0.40	0.38	-0.01	-0.01	0.00	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	0.30	0.27	0.28	0.33	0.33	0.23	0.25	0.37	0.36	0.35	-0.02	-0.00	0.00	0.53	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	0.20	0.19	0.19	0.22	0.21	0.15	0.16	0.23	0.23	0.23	-0.00	0.01	-0.00	0.32	0.53	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20	-	-	-	-0.00	-0.01	-0.01	-0.01	-0.00	-0.00	-0.00	-0.00	0.00	-0.01	-0.01	-0.00	-0.01	-0.00	-0.00	-0.01	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21	-	-	-	-0.01	-0.01	-0.01	-0.00	0.00	0.00	-0.00	-0.00	0.01	0.02	0.00	-0.00	0.00	0.02	-0.00	-0.01	0.02	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	0.91	0.91	0.08	0.09	0.10	0.07	0.08	0.12	0.12	0.11	-0.00	-0.00	-0.03	0.16	0.27	0.18	-0.01	-0.01	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-
23	-	-	-	0.13	0.12	0.27	0.33	0.37	0.22	0.23	0.42	0.26	0.25	-0.00	-0.00	0.00	0.66	0.34	0.21	0.00	0.00	0.11	1.00	-	-	-	-	-	-	-	-	-	-	-	-
24	-	-	-	0.17	0.15	0.45	0.54	0.44	0.37	0.41	0.46	0.57	0.57	-0.01	0.00	-0.00	0.48	0.44	0.30	0.00	0.01	0.14	0.31	1.00	-	-	-	-	-	-	-	-	-	-	-
25	-	-	-	0.10	0.10	0.49	0.58	0.43	0.39	0.45	0.43	0.32	0.33	-0.02	0.02	0.01	0.35	0.28	0.19	-0.01	-0.00	0.09	0.23	0.54	1.00	-	-	-	-	-	-	-	-	-	-
26	-	-	-	0.11	0.10	0.22	0.26	0.23	0.17	0.20	0.25	0.30	0.29	-0.01	-0.01	-0.02	0.30	0.27	0.18	-0.02	0.01	0.09	0.21	0.45	0.25	1.00	-	-	-	-	-	-	-	-	-
27	-	-	-	0.87	0.79	0.12	0.14	0.14	0.10	0.11	0.15	0.17	0.15	0.00	-0.02	-0.03	0.21	0.35	0.24	0.00	-0.00	0.79	0.15	0.20	0.13	0.12	1.00	-	-	-	-	-	-	-	-
28	-	-	-	0.93	0.85	0.11	0.13	0.12	0.09	0.10	0.14	0.15	0.14	0.01	-0.01	-0.04	0.20	0.32	0.22	-0.00	-0.01	0.85	0.14	0.18	0.11	0.11	0.93	1.00	-	-	-	-	-	-	-
29	-	-	-	0.93	0.85	0.09	0.11	0.11	0.08	0.09	0.13	0.13	0.12	0.01	-0.01	-0.03	0.17	0.28	0.19	-0.00	-0.01	0.85	0.12	0.15	0.09	0.10	0.81	0.87	1.00	-	-	-	-	-	-
30	-	-	-	0.86	0.79	0.10	0.11	0.12	0.07	0.09	0.13	0.13	0.13	0.01	-0.00	-0.03	0.18	0.29	0.20	0.00	-0.01	0.79	0.13	0.16	0.10	0.10	0.86	0.92	0.80	1.00	-	-	-	-	-
31	-	-	-	0.22	0.20	0.36	0.44	0.43	0.29	0.33	0.47	0.56	0.55	-0.01	0.01	0.00	0.65	0.58	0.40	0.00	0.02	0.20	0.42	0.62	0.39	0.42	0.26	0.24	0.21	0.22	1.00	-	-	-	-
32	-	-	-	0.72	0.66	0.15	0.18	0.16	0.12	0.14	0.19	0.19	0.18	-0.00	-0.01	-0.02	0.26	0.43	0.30	-0.00	0.00	0.66	0.18	0.24	0.15	0.14	0.83	0.77	0.67	0.71	0.31	1.00	-	-	-
33	-	-	-	0.67	0.61	0.14	0.16	0.14	0.11	0.12	0.17	0.17	0.16	-0.00	-0.02	-0.02	0.24	0.39	0.27	-0.01	-0.00	0.61	0.17	0.21	0.14	0.12	0.77	0.72	0.62	0.66	0.29	0.93	1.00	-	-
34	-	-	-	0.18	0.15	0.28	0.33	0.29	0.23	0.25	0.31	0.35	0.35	-0.02	0.00	0.02	0.37	0.47	0.33	0.01	0.00	0.15	0.24	0.55	0.32	0.26	0.21	0.19	0.16	0.18	0.45	0.26	0.23	1.00	-
35	-	-	-	0.35	0.32	0.30	0.36	0.34	0.24	0.26	0.38	0.40	0.39	-0.01	0.00	-0.00	0.53	0.86	0.61	-0.01	0.01	0.31	0.35	0.49	0.30	0.30	0.41	0.37	0.33	0.34	0.64	0.50	0.45	0.53	1.00

Key to parameter codes:
Absolute change:
1: Insulin glargine-metformin – Mean; 2: Insulin glargine-metformin – Pred; 3: Insulin glargine-metformin – Beta
Relative effects:
4: Acarbose-metformin-sulfonylurea; 5: Biphasic human insulin-NPH insulin; 6: Biphasic insulin aspart; 7: Biphasic insulin aspart-metformin; 8: Biphasic insulin aspart-metformin-sulfonylurea; 9: Biphasic insulin aspart-pioglitazone; 10: Biphasic insulin aspart-repaglinide; 11: Exenatide-metformin-sulfonylurea; 12: Insulin aspart (short acting); 13: Insulin aspart (short acting)-metformin; 14: Insulin degludec/aspart mix-metformin; 15: Insulin degludec-metformin; 16: Insulin detemir-metformin; 17: Insulin glargine-metformin-sulfonylurea; 18: Insulin glargine-sulfonylurea; 19: Insulin lispro

mix 50 and mix 25; 20: Insulin lispro mix 50/50-metformin; 21: Insulin lispro mix 75/25-metformin; 22: Insulin lispro-metformin; 23: Liraglutide-metformin-sulfonylurea; 24: Metformin-NPH insulin; 25: Metformin-NPH insulin mix 70/30; 26: Metformin-NPH insulin-repaglinide; 27: Metformin-NPH insulin-sulfonylurea; 28: Metformin-pioglitazone-sulfonylurea; 29: Metformin-repaglinide-sulfonylurea; 30: Metformin-sitagliptin-sulfonylurea; 31: NPH insulin; 32: NPH insulin mix 70/30; 33: NPH insulin mix 70/30-sulfonylurea; 34: NPH insulin-repaglinide; 35: NPH insulin-sulfonylurea

Table 53: Safety and efficacy data inputs for health economic model – second intensification – weight at 1 year

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Mean	1.703	n/a	1.232	4.445	3.390	6.958	-1.824	-0.543	-0.088	-2.093	-0.600	2.278	2.689	2.157	1.099	-1.121	1.912	2.113	2.734	4.334	1.131	2.796	5.308	5.763	1.555	1.939
SD	0.255	-	1.211	0.980	0.839	1.264	0.798	0.684	0.610	0.585	0.502	0.738	0.688	0.827	0.604	0.878	1.035	0.976	1.199	1.245	1.284	0.714	1.127	1.261	0.510	0.639
	Correlation matrix																									
1	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	0.231	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	0.263	0.822	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	0.178	0.777	0.641	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	0.281	0.821	0.957	0.642	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	0.004	0.001	0.001	0.001	0.001	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	-0.016	-0.000	-0.011	-0.001	-0.010	0.612	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	-0.012	0.000	-0.004	-0.006	-0.005	0.631	0.700	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-0.011	0.003	-0.006	0.005	-0.006	0.739	0.819	0.858	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	0.308	0.756	0.881	0.592	0.920	0.006	-0.012	-0.002	-0.004	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	0.368	0.510	0.592	0.399	0.621	0.009	-0.008	-0.001	-0.002	0.684	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	0.310	0.352	0.405	0.276	0.430	0.021	-0.001	0.008	0.008	0.474	0.675	1.000	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-0.005	-0.009	-0.017	-0.007	-0.016	0.612	0.672	0.709	0.826	-0.013	-0.007	-0.002	1.000	-	-	-	-	-	-	-	-	-	-	-
16	-	-	0.256	0.635	0.741	0.500	0.775	0.005	-0.011	-0.011	-0.009	0.845	0.580	0.404	-0.010	1.000	-	-	-	-	-	-	-	-	-	-
17	-	-	0.112	0.224	0.262	0.169	0.274	0.001	0.001	0.011	0.005	0.298	0.215	0.153	0.002	0.246	1.000	-	-	-	-	-	-	-	-	-
18	-	-	0.799	0.294	0.334	0.232	0.354	0.003	-0.014	-0.014	-0.012	0.388	0.466	0.388	-0.015	0.319	0.138	1.000	-	-	-	-	-	-	-	-
19	-	-	0.993	0.234	0.268	0.180	0.286	0.004	-0.016	-0.012	-0.010	0.313	0.373	0.314	-0.006	0.260	0.113	0.806	1.000	-	-	-	-	-	-	-
20	-	-	0.972	0.222	0.256	0.171	0.273	0.001	-0.018	-0.016	-0.014	0.300	0.356	0.301	-0.007	0.249	0.110	0.776	0.966	1.000	-	-	-	-	-	-
21	-	-	0.928	0.219	0.249	0.169	0.267	0.004	-0.018	-0.014	-0.012	0.295	0.349	0.297	-0.009	0.245	0.109	0.753	0.934	0.903	1.000	-	-	-	-	-
22	-	-	0.311	0.658	0.767	0.518	0.800	0.008	-0.006	0.001	-0.002	0.865	0.623	0.442	-0.008	0.732	0.343	0.392	0.315	0.301	0.296	1.000	-	-	-	-
23	-	-	0.521	0.262	0.293	0.204	0.312	-0.001	-0.014	-0.021	-0.017	0.343	0.429	0.360	-0.016	0.290	0.120	0.653	0.526	0.505	0.494	0.340	1.000	-	-	-
24	-	-	0.469	0.233	0.259	0.178	0.278	-0.008	-0.020	-0.023	-0.020	0.303	0.379	0.318	-0.019	0.258	0.104	0.582	0.472	0.453	0.444	0.299	0.897	1.000	-	-
25	-	-	0.223	0.269	0.308	0.216	0.324	0.006	-0.003	-0.001	0.003	0.354	0.484	0.426	0.002	0.288	0.106	0.289	0.225	0.217	0.211	0.332	0.257	0.235	1.000	-
26	-	-	0.407	0.469	0.542	0.364	0.571	0.014	-0.004	-0.001	0.001	0.632	0.882	0.771	-0.007	0.534	0.200	0.514	0.413	0.395	0.386	0.590	0.476	0.422	0.556	1.000

Key to parameter codes:
Absolute change:
1: Metformin-NPH insulin - Mean; 2: Metformin-NPH insulin - Pred
Relative effects:
3: Acarbose-metformin-sulfonylurea; 4: Biphasic insulin aspart-metformin; 5: Biphasic insulin aspart-metformin-sulfonylurea; 6: Biphasic insulin aspart-repaglinide; 7: Exenatide-metformin-sulfonylurea; 8: Insulin degludec/aspart mix-metformin; 9: Insulin degludec-metformin; 10: Insulin detemir-metformin; 11: Insulin glargine-metformin; 12: Insulin glargine-metformin-sulfonylurea; 13: Insulin glargine-sulfonylurea; 14: Insulin lispro mix 50 and mix 25; 15: Insulin lispro mix 50/50-metformin; 16: Liraglutide-metformin-sulfonylurea; 17: Metformin-NPH insulin-repaglinide; 18: Metformin-NPH insulin-sulfonylurea; 19: Metformin-pioglitazone-sulfonylurea; 20: Metformin-repaglinide-sulfonylurea; 21: Metformin-sitagliptin-sulfonylurea; 22: NPH insulin; 23: NPH insulin mix 70/30; 24: NPH insulin mix 70/30-sulfonylurea; 25: NPH insulin-repaglinide; 26: NPH insulin-sulfonylurea

Table 54: Safety and efficacy data inputs for health economic model – second intensification – incidence of hypoglycaemia (annual rate)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Mean	0.675	0.691	0.484	0.778	0.786	0.523	0.310	1.040	-0.580	0.083	0.749	0.403	0.640	-0.769	-0.656	-0.326	0.032	0.026	1.694	0.526	-0.549	0.290	0.548	0.480	-0.446	-0.274	0.952	1.290	-0.16	0.274
SD	0.642	1.679	0.252	0.504	0.394	0.443	0.633	0.540	0.547	0.392	0.415	0.413	0.538	0.559	0.477	0.290	0.311	0.293	0.499	0.472	0.495	0.504	0.656	0.370	0.511	0.892	0.537	0.610	0.320	0.263
	Correlation matrix																													
1	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	0.145	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	0.189	0.788	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	0.253	0.510	0.648	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	0.113	0.792	0.628	0.404	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	0.137	0.584	0.733	0.474	0.451	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	0.286	0.156	0.201	0.262	0.121	0.142	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	0.304	0.500	0.628	0.790	0.395	0.462	0.327	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	0.317	0.060	0.067	0.084	0.043	0.057	0.097	0.096	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	0.321	0.050	0.052	0.071	0.044	0.049	0.088	0.089	0.402	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	0.139	0.072	0.082	0.121	0.040	0.051	0.124	0.142	0.044	0.050	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	0.141	0.055	0.074	0.125	0.035	0.056	0.123	0.141	0.050	0.049	0.291	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	0.164	0.059	0.082	0.119	0.028	0.050	0.143	0.151	0.050	0.050	0.335	0.335	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	0.272	0.105	0.138	0.202	0.061	0.092	0.235	0.248	0.086	0.091	0.538	0.537	0.608	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	0.490	0.284	0.367	0.484	0.220	0.264	0.558	0.599	0.155	0.142	0.216	0.213	0.238	0.400	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	0.489	0.144	0.186	0.250	0.104	0.131	0.276	0.294	0.141	0.154	0.216	0.220	0.259	0.411	0.497	1.000	-	-	-	-	-	-	-	-	-	-	-	-
19	-	-	0.324	0.071	0.094	0.133	0.053	0.064	0.139	0.151	0.098	0.119	0.077	0.089	0.108	0.176	0.241	0.403	1.000	-	-	-	-	-	-	-	-	-	-	-
20	-	-	0.159	0.070	0.087	0.127	0.051	0.049	0.142	0.148	0.060	0.054	0.330	0.335	0.357	0.610	0.242	0.237	0.086	1.000	-	-	-	-	-	-	-	-	-	-
21	-	-	0.312	0.187	0.237	0.307	0.141	0.178	0.343	0.367	0.092	0.095	0.121	0.130	0.142	0.235	0.633	0.306	0.150	0.144	1.000	-	-	-	-	-	-	-	-	-
22	-	-	0.091	0.341	0.432	0.280	0.266	0.318	0.097	0.274	0.046	0.028	0.040	0.021	0.043	0.062	0.173	0.085	0.045	0.022	0.111	1.000	-	-	-	-	-	-	-	-
23	-	-	-0.000	0.008	0.005	0.000	0.007	-0.005	-0.017	-0.007	0.009	0.003	-0.009	-0.005	0.010	-0.003	-0.018	-0.012	-0.013	0.006	-0.022	0.000	1.000	-	-	-	-	-	-	-
24	-	-	0.405	0.097	0.114	0.134	0.082	0.086	0.141	0.156	0.132	0.136	0.091	0.078	0.107	0.160	0.251	0.307	0.203	0.089	0.150	0.052	0.005	1.000	-	-	-	-	-	-
25	-	-	0.289	0.078	0.091	0.098	0.064	0.070	0.095	0.117	0.097	0.111	0.065	0.059	0.084	0.119	0.169	0.220	0.158	0.063	0.085	0.047	0.005	0.728	1.000	-	-	-	-	-
26	-	-	0.183	0.055	0.059	0.069	0.049	0.052	0.051	0.076	0.059	0.067	0.049	0.029	0.041	0.065	0.099	0.141	0.107	0.032	0.034	0.022	0.008	0.421	0.576	1.000	-	-	-	-
27	-	-	0.279	0.058	0.069	0.090	0.052	0.055	0.093	0.106	0.095	0.103	0.073	0.063	0.073	0.113	0.177	0.205	0.132	0.050	0.110	0.033	0.000	0.689	0.495	0.278	1.000	-	-	-
28	-	-	0.249	0.047	0.064	0.082	0.040	0.050	0.085	0.093	0.084	0.093	0.067	0.054	0.071	0.102	0.152	0.179	0.118	0.048	0.089	0.034	0.001	0.608	0.437	0.242	0.879	1.000	-	-
29	-	-	0.245	0.028	0.054	0.084	0.026	0.026	0.101	0.110	0.069	0.072	0.076	0.076	0.092	0.148	0.200	0.338	0.203	0.085	0.126	0.021	-0.011	0.165	0.127	0.079	0.102	0.092	1.000	-
30	-	-	0.587	0.130	0.173	0.238	0.102	0.120	0.249	0.278	0.182	0.191	0.174	0.177	0.203	0.325	0.449	0.767	0.540	0.183	0.279	0.077	-0.013	0.390	0.281	0.182	0.259	0.227	0.426	1.000

Key to parameter codes:
Baseline ln(rate):
1: Metformin-NPH insulin - Mean; 2: Metformin-NPH insulin – Pred
Relative effects – ln(HR):
3: NPH insulin; 4: Biphasic insulin aspart; 5: Biphasic insulin aspart-metformin; 6: Biphasic insulin aspart-metformin-sulfonylurea; 7: Biphasic insulin aspart-pioglitazone; 8: Biphasic insulin aspart-repaglinide; 9: Exenatide (once weekly)-metformin-sulfonylurea; 10: Exenatide-metformin-sulfonylurea; 11: Insulin aspart (short acting); 12: Insulin aspart (short acting)-metformin; 13: Insulin degludec/aspart mix-metformin; 14: Insulin degludec-metformin; 15: Insulin detemir-metformin; 16: Insulin glargine-metformin; 17: Insulin glargine-metformin-sulfonylurea; 18: Insulin glargine-sulfonylurea; 19: Insulin lispro mix 50 and mix 25; 20: Insulin lispro mix 50/50-metformin; 21: Liraglutide-metformin-sulfonylurea; 22: Metformin-NPH insulin mix 70/30; 23: Metformin-NPH insulin-repaglinide; 24: Metformin-NPH insulin-sulfonylurea; 25: Metformin-pioglitazone-sulfonylurea; 26: Metformin-sitagliptin-sulfonylurea; 27: NPH insulin mix 70/30; 28: NPH insulin mix 70/30-sulfonylurea; 29: NPH insulin-repaglinide; 30: NPH insulin-sulfonylurea

Table 55: Safety and efficacy data inputs for health economic model – second intensification – dropouts due to AEs (annual rate)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Mean	-2.631	n/a	-1.322	-0.138	0.349	-2.687	-1.104	3.122	0.625	-0.487	-0.823	1.501	-0.666	0.368	-0.215	-2.851	-1.407	-3.432	1.873	-1.984	-1.898	0.844	-1.313	-1.322	-2.278	-2.390	-1.67	-1.29
SD	0.295	-	2.135	1.445	1.027	1.426	2.088	2.597	1.055	0.729	0.819	2.963	2.170	1.942	1.795	1.003	1.196	1.739	2.267	1.149	2.343	1.606	1.090	2.108	2.602	2.598	0.736	1.085
	Correlation matrix																											
1	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	0.018	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	0.014	0.707	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	0.014	0.471	0.658	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	0.008	0.694	0.488	0.326	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	-0.002	0.285	0.405	0.257	0.201	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	0.008	0.624	0.883	0.725	0.427	0.354	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	0.004	0.045	0.058	0.050	0.022	0.021	0.068	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	0.019	0.045	0.063	0.044	0.016	0.018	0.063	0.314	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	-0.007	-0.007	0.003	-0.009	0.003	0.008	-0.005	-0.014	-0.005	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13	-	-	0.016	-0.008	0.005	0.006	0.006	0.017	-0.007	0.005	-0.001	0.501	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	0.010	-0.021	-0.011	-0.010	-0.007	0.008	-0.019	0.003	-0.007	0.550	0.760	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	0.008	-0.018	-0.006	-0.003	-0.005	0.005	-0.013	0.006	-0.007	0.601	0.834	0.917	1.000	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	0.023	0.378	0.534	0.438	0.258	0.222	0.602	0.102	0.088	-0.012	-0.017	-0.016	-0.015	1.000	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	0.103	0.034	0.043	0.040	0.030	0.009	0.046	0.020	0.016	0.000	0.002	-0.004	-0.004	0.065	1.000	-	-	-	-	-	-	-	-	-	-	-
18	-	-	0.073	0.028	0.024	0.031	0.034	-0.007	0.029	0.012	0.007	0.009	0.013	0.008	0.008	0.044	0.556	1.000	-	-	-	-	-	-	-	-	-	-
19	-	-	0.009	-0.018	-0.008	-0.005	-0.013	-0.004	-0.016	0.006	-0.001	0.484	0.667	0.733	0.796	-0.015	-0.014	-0.002	1.000	-	-	-	-	-	-	-	-	-
20	-	-	0.013	0.332	0.469	0.387	0.232	0.195	0.528	0.086	0.077	-0.008	-0.013	-0.013	-0.014	0.872	0.048	0.034	-0.013	1.000	-	-	-	-	-	-	-	-
21	-	-	-0.001	0.163	0.238	0.162	0.103	0.094	0.212	0.007	0.021	0.015	-0.001	-0.002	-0.006	0.127	0.026	0.012	0.001	0.115	1.000	-	-	-	-	-	-	-
22	-	-	0.012	0.019	0.041	0.040	0.012	0.010	0.048	0.027	0.016	0.004	0.002	0.001	0.001	0.065	0.028	0.012	0.010	0.052	0.007	1.000	-	-	-	-	-	-
23	-	-	0.507	0.036	0.042	0.038	0.025	0.005	0.044	-0.002	0.015	0.000	0.013	0.006	0.004	0.071	0.188	0.135	0.000	0.057	0.011	0.022	1.000	-	-	-	-	-
24	-	-	0.986	0.016	0.010	0.010	0.006	-0.005	0.005	0.005	0.017	-0.007	0.013	0.008	0.006	0.023	0.109	0.077	0.006	0.012	-0.001	0.014	0.516	1.000	-	-	-	-
25	-	-	0.820	0.006	-0.001	0.005	-0.008	-0.005	-0.008	0.000	0.011	0.000	0.015	0.014	0.013	0.008	0.086	0.065	0.011	0.000	0.001	0.003	0.408	0.809	1.000	-	-	-
26	-	-	0.802	0.011	0.007	0.003	0.006	-0.010	0.004	0.008	0.016	-0.002	0.010	0.011	0.008	0.010	0.089	0.062	0.003	0.003	-0.006	0.017	0.412	0.812	0.659	1.000	-	-
27	-	-	0.066	0.223	0.307	0.255	0.144	0.124	0.348	0.157	0.161	-0.006	-0.016	-0.012	-0.015	0.571	0.107	0.064	-0.015	0.492	0.086	0.093	0.126	0.069	0.049	0.045	1.000	-
28	-	-	0.112	0.031	0.042	0.042	0.033	0.010	0.049	0.025	0.014	-0.001	0.002	-0.001	-0.002	0.068	0.914	0.607	-0.011	0.050	0.019	0.031	0.201	0.116	0.090	0.093	0.114	1.000

Key to parameter codes:
Baseline ln(rate):
1: Metformin-NPH insulin - Mean; 2: Metformin-NPH insulin – Pred
Relative effects – ln(HR):
3: Acarbose-metformin-sulfonylurea; 4: Biphasic insulin aspart; 5: Biphasic insulin aspart-metformin; 6: Biphasic insulin aspart-metformin-sulfonylurea; 7: Biphasic insulin aspart-pioglitazone; 8: Biphasic insulin aspart-repaglinide; 9: Exenatide-metformin-sulfonylurea; 10: Insulin aspart (short acting); 11: Insulin aspart (short acting)-metformin; 12: Insulin degludec/aspart mix-metformin; 13: Insulin degludec-metformin; 14: Insulin detemir-metformin; 15: Insulin glargine-metformin; 16: Insulin glargine-metformin-sulfonylurea; 17: Insulin glargine-sulfonylurea; 18: Insulin lispro mix 50 and mix 25; 19: Insulin lispro mix 50/50-metformin; 20: Liraglutide-metformin-sulfonylurea; 21: Metformin-NPH insulin mix 70/30; 22: Metformin-NPH insulin-repaglinide; 23: Metformin-NPH insulin-sulfonylurea; 24: Metformin-pioglitazone-sulfonylurea; 25: Metformin-repaglinide-sulfonylurea; 26: Metformin-sitagliptin-sulfonylurea; 27: NPH insulin; 28: NPH insulin-sulfonylurea

3.7 Absolute treatment effects modelled

For reference purposes, it is useful to summarise the absolute treatment effects used in the original health economic model here for initial therapy (see table 56), first intensification (see table 57) and second intensification (see table 58). Only those treatments for which the minimum dataset was available are listed here.

Table 56: Absolute treatment effects modelled – initial therapy

Treatment	HbA1c at 1yr (reduction in %)[a]	Weight-change at 1yr (kg)	Probability of dropout due to intolerance	Annual rate all hypoglycaemic episodes
Metformin	-0.789	-2.101	0.075	0.194
Pioglitazone	-0.750	+1.357	0.082	0.194
Placebo	+0.050	+0.391	0.052	0.129
Repaglinide	-0.834	+1.091	0.034	0.674
Sitagliptin	-0.626	-0.263	0.054	0.160
Sulfonylurea	-0.636	+1.491	0.088	0.794
Vildagliptin	-0.332	+0.095	0.051	0.146

(a) HbA1c reductions based on an individual with baseline Hba1c equal to 7.5%

Table 57: Absolute treatment effects modelled – first intensification

Treatment	HbA1c at 1yr (reduction in %)[a]	Weight-change at 1yr (kg)	Probability of dropout due to intolerance	Annual rate all hypoglycaemic episodes
Exenatide-metformin	-0.466	-2.848	0.086	0.292
Linagliptin-metformin	-0.563	-1.246	0.034	0.111
Liraglutide-metformin	-0.809	-3.090	0.152	0.197
Metformin-pioglitazone	-0.704	+1.907	0.056	0.065
Metformin-sitagliptin	-0.462	-1.127	0.057	0.131
Metformin-sulfonylurea	-0.665	+1.354	0.041	1.014
Metformin-vildagliptin	-0.629	-0.441	0.047	0.329

(a) HbA1c reductions based on an individual with baseline Hba1c equal to 7.5%

Table 58: Absolute treatment effects modelled - second intensification

Treatment	HbA1c at 1yr (reduction in %)[a]	Weight-change at 1yr (kg)	Probability of dropout due to intolerance	Annual rate all hypoglycaemic episodes
Biphasic insulin aspart-metformin	-0.853	+6.149	0.097	23.967
Biphasic insulin aspart-metformin-sulfonylurea	-0.416	+5.094	0.005	18.436
Biphasic insulin aspart-repaglinide	-0.659	+8.662	0.805	30.889
Exenatide-metformin-sulfonylurea	-0.325	-0.121	0.126	11.863
Insulin degludec/aspart mix-metformin	-0.232	+1.161	0.276	20.722
Insulin degludec-metformin	-0.016	+1.615	0.036	5.063
Insulin detemir-metformin	+0.105	-0.390	0.099	5.669
Insulin glargine-metformin	-0.147	+1.103	0.056	7.886
Insulin glargine-metformin-sulfonylurea	-0.476	+3.981	0.004	11.282
Insulin glargine-sulfonylurea	+0.154	+4.393	0.017	11.214
Insulin lispro mix 50 and mix 25	-0.476	+3.860	0.002	59.442
Insulin lispro mix 50/50-metformin	-0.546	+2.802	0.374	18.487
Liraglutide-metformin-sulfonylurea	-0.715	+0.582	0.010	6.306
Metformin-NPH insulin	-0.535	+1.703	0.070	10.922
Metformin-NPH insulin-repaglinide	-1.794	+3.615	0.154	18.899
Metformin-NPH insulin-sulfonylurea	+0.904	+3.816	0.019	17.645
Metformin-pioglitazone-sulfonylurea	+1.307	+4.437	0.019	6.992
Metformin-sitagliptin-sulfonylurea	+1.538	+2.834	0.007	8.308
NPH insulin	-0.162	+4.499	0.013	17.725
NPH insulin-sulfonylurea	+0.318	+3.642	0.020	14.362

(a) HbA1c reductions based on an individual with baseline Hba1c equal to 7.5%

3.8 Resource use and unit costs

All resource use and costs were measured from an NHS and PSS perspective (National Institute for Health and Care Excellence 2012b) and costs were inflated to 2012–13 prices (Curtis 2014). Resource use and costs used in the original health economic model are in 2 categories – longer-term outcomes and drug related resource use and costs.

3.8.1 Long-term outcome resource use and costs

As explained in 3.2.1, we used UKPDS OM1 to model macrovascular and microvascular complication events. For our estimate of the costs associated with these events and their ensuing treatment, we used the UKPDS RCT (Clarke et al. 2003) for all events other than renal failure (for which reliable costs are not available in the UKPDS RCT; see below). UKPDS costs estimate the annual cost of care for people who have experienced the outcomes modelled (separately for the year of the event and subsequent years), cover future healthcare resource use and costs for inpatient and non-inpatient care (including primary care) but do not cover any drug costs. This source also provides a value for the background healthcare costs of people with type 2 diabetes who do not experience any complications in a given year.

We used UKPDS RCT costs for 2 main reasons. Firstly, using the same source for the generation and costing of longer term outcomes ensured their definitions matched, reducing uncertainty within the original health economic model. Secondly, UKPDS RCT covered people on a variety of treatment options. As longer term outcome costs specific to each treatment option were not available, a source that covered a variety of treatment options used in clinical practice was beneficial.

We discussed some limitations of the UKPDS RCT costs with the GDG. As noted when considering model selection (see 3.1), the UKPDS RCT took place a number of years ago, enrolled people with newly diagnosed type 2 diabetes only and covered only a limited set of first outcomes. Another limitation is that the available cost calculations are based on an average-aged man (59 years) and have not been varied by therapy level. It is conceivable that costs may differ for older people, women or people on different therapy levels. Costs of multiple events were treated additively – this may be an over-count but is an assumption that has not been explored in the literature.

We could have used other, more recent complication cost data (Clarke et al. 2010), but these would not have directly matched the long-term outcome definitions in UKPDS OM1 and also would have been a departure from previous guidelines. Also, more recent type diabetes specific cost data may not have been available for all complications. Updated UKPDS RCT costs were due to be published shortly after this guideline and should be considered for use in future work.

We took renal failure costs from a different bottom-up UK study (Lamping et al. 2000). This was the source recommended for use with UKPDS OM1 (Clarke et al. 2004); it is necessary to look elsewhere for these data because not enough renal failure events occurred within the UKPDS RCT to allow costs (or utilities) to be estimated. Lamping et al. (2000) did not limit their analysis to type 2 diabetes, but they analysed people with type 2 diabetes as a subgroup and found costs not to differ. Lamping et al. (2000) only considered inpatient costs, so UKPDS non-inpatient macrovascular costs were added.

We extracted UKPDS RCT long-term outcome costs from their original papers and inflated them to 2012–13 costs using recommended inflation estimates (see table 59) (Curtis 2014). This allowed accurate measures of dispersion to be taken from the original sources and also avoided errors due to rounding or intermediate use of provisional inflation indices. This had limited impact on most outcome costs, but impacted renal failure costs.

A frequently sourced cost for renal failure is £30,000 per annum in 2004 prices (Clarke et al. 2004), which when inflated equates to £37,335 in 2012–13 prices. This cost is usually applied for both the year of the event and subsequent years. However, inflating the £21,117 source cost in 1996 prices (Lamping et al. 2000) (£20,802 inpatient cost of renal failure plus £315 UKPDS non-inpatient year of macrovascular event cost, see table 59) gives £35,715 in 2012–13 prices (£1620 less) (Curtis 2007). Unlike other CUAs, the original health economic model also slightly differentiated between renal failure costs for the initial and subsequent years. UKPDS had slightly different non-inpatient costs for the year of macrovascular events (£315) and subsequent years (£258) and as a result the 2012–13 cost of renal failure in subsequent years was £35,631 (£1704 less).

We believe that directly using the source data produces more accurate estimates than inflating the intermediate 2004 cost. For renal failure, the differences between this and previous approaches were not insubstantial; renal failure rates were low in UKPDS OM1 but renal failure was the most costly outcome. It should be noted that the 2012–13 inflation figure used was provisional and future work should use the most up–to-date inflation figures, rather than inflating from intermediate figures.

Table 59: UKPDS OM1 long term outcome costs: source and 2012-13 costs

		Source cost			2012–13 costs
Event Type	**Outcome**	**Inpatient**	**Non-Inpatient**	**Total**	**Total**
Non-fatal event – year of event	No complication	£157	£159	£316	£465
	IHD	£1959	£315	£2274	£3346
	MI	£4070	£315	£4385	£6451
	CHF	£2221	£315	£2536	£3731
	Stroke	£2367	£315	£2682	£3946
	Amputation	£8459	£273	£8732	£12,847
	Blindness	£872	£273	£1145	£1685
	Renal failure	*£20,802*	*£315*	*£21,117*	*£35,715*
Non-fatal event – subsequent years	IHD	£493	£258	£751	£1105
	MI	£464	£258	£722	£1062
	CHF	£631	£258	£889	£1308
	Stroke	£249	£258	£507	£746
	Amputation	£300	£204	£504	£742
	Blindness	£281	£204	£485	£714
	Renal failure	*£20,802*	*£258*	*£21,060*	*£35,631*
Fatal event – year of event	MI	–	–	£1152	£1695
	CHF	–	–	£2536	£3731
	Stroke	–	–	£3383	£4977
	Amputation	–	–	£8732	£12,847
	Renal failure	–	–	*£21,117*	*£35,715*

(b) 2012 costs rounded to nearest pound
(c) Source year for all outcomes except inpatient renal failure was 2000, source year for inpatient renal failure was 1996
(d) Where fatal event costs are not listed, these were not included in UKPDS costs paper (Clarke et al. 2004)
(e) IHD = ischaemic heart disease, MI = myocardial infarction, CHF = congestive heart failure, Renal failure = end stage renal failure

3.8.2 Drug resource use

Resource use associated with modelled treatment options included the drugs themselves, associated consumables and NHS staff time.

In calculating drug costs, the dosages we used were taken from included RCTs to ensure each treatment option cost was directly related to magnitude of treatment effect. Across different arms, drug doses were weighted according to included RCT participant numbers. As most trials included a dose titration period, this was reflected in the resource use and cost of drugs. We calculated a separate average daily dose and cost for year 1, based on the reported titration periods in each arm. If dose titration was reported without the time period being specified or as stepped across a number of weeks or months, the mid-point of the RCT was used. Some RCTs titrated exenatide from 5mcg to 10mcg, but the unit cost for both doses was the same; therefore, no adjustment was necessary.

It is important to note that using weighted average dosages from included RCTs represents a departure from the previous guideline, where assumed daily doses were used. We believe that using the weighted average dose from included RCTs better reflects the link between dosage and magnitude of treatment effect. While it is true that some treatments may be used at different dosages in practice to those seen on average in included RCTs, this implies that the efficacy and safety of those treatments would also be different. We tested the impact of this assumption in sensitivity analysis; see 3.11.2.3.

A number of adjustments and assumptions were necessary to ensure weighted average doses could be calculated for all treatment options.

Whilst glimepiride was the most commonly used sulfonylurea in the included RCTs, the GDG advised that gliclazide was the most commonly used sulfonylurea in the NHS. This was supported by prescription data (see table 60). For RCTs where other sulfonylureas were used, doses were converted to an equivalent dose of gliclazide, based on World Health Organisation (WHO) defined daily doses (World Health Organisation 2014) and in agreement with the GDG (see table 61).

Table 60: Sulfonylureas prescribed by type (England, 2013)

Sulfonylurea	Percentage
Gliclazide	90.67%
Glimepiride	5.28%
Glipizide	2.07%
Glibenclamide	1.05%
Tolbutamide	0.94%

(a) Percentages based on quantities prescribed
(b) Source: Health and Social Information Centre (2013)

Table 61: Doses assumed to be equivalent to 160mg daily dose of gliclazide

Sulfonylurea	Gliclazide 160mg equivalent dose
Glibenclamide	10mg
Glimepiride	4mg
Glipizide	20mg

(a) No included RCTs involved tolbutamide

Where included RCTs did not report dosage, the weighted average of reporting RCTs was used (see table 62). None of the included initial therapy RCTs with repaglinide arms reported dosage; average repaglinide dose was calculated from 5 excluded RCTs (Fang et al. 2014; Jovanovic et al. 2000a; Jovanovic et al. 2000b; Jovanovic et al. 2004; Lund et al. 2007; Lund et al. 2008). The GDG agreed that 4mg was an appropriate daily dose for repaglinide and this was also the dose used in assumed daily dose sensitivity analysis (see 3.11.2.3).

It should be noted that included RCTs involving NPH insulin (+/- oral drugs) displayed a particularly wide range of daily doses (20–80 units/day). Given the sparseness of the second intensification NMA, such anomalies were necessarily not corrected by dose averaging

across multiple RCTs, but were another justification for using RCT-based doses rather than assumed daily doses.

Table 62: Weighted average dose per day in included RCTs

Therapy level	Treatment option	Drug	Average dose per day
Initial Therapy	Metformin	Metformin	1751.5mg
	Pioglitazone	Pioglitazone	43.4mg
	Repaglinide	Repaglinide	3.96mg
	Sitagliptin	Sitagliptin	84.3mg
	Sulfonylurea	Sulfonylurea	159.3mg
	Vildagliptin	Vildagliptin	93.6mg
First Intensification	Exenatide-metformin	Exenatide	No missing data
		Metformin	2000mg[b]
	Linagliptin-metformin	Linagliptin	No missing data
		Metformin	1500mg
	Liraglutide-metformin	Liraglutide	No missing data
		Metformin	2000mg
	Metformin-pioglitazone	Metformin	1822.6mg
		Pioglitazone	35.6mg
	Metformin-saxagliptin	Metformin	1926.3mg[c]
		Saxagliptin	No missing data
	Metformin-sitagliptin	Metformin	1926.3mg[c]
		Sitagliptin	No missing data
	Metformin-sulfonylurea	Metformin	1858.6mg
		Sulfonylurea	143.6mg
	Metformin-vildagliptin	Metformin	1926.3mg
		Vildagliptin	No missing data
	Pioglitazone-sulfonylurea	Pioglitazone	37.0mg
		Sulfonylurea	143.6mg[d]

(a) "No missing data" means all included RCTs for that treatment option reported drug dose, therefore no drug doses had to be estimated for these treatment options
(b) No exenatide-metformin RCTs reported metformin dose, so metformin dose was taken from liraglutide-metformin RCTs
(c) No metformin-saxagliptin RCTs or metformin-sitagliptin RCTs reported metformin dose, so metformin dose was taken from metformin-vildagliptin RCTs (as more participants than linagliptin-metformin RCTs)
(d) No pioglitazone-sulfonylurea RCTs reported sulfonylurea dose, so sulfonylurea dose was taken from metformin-sulfonylurea RCTs
(e) No second intensification RCTs failed to report drug doses

Some included RCTs reported insulin dosage as units/kilogram body weight/day. Where the RCTs also reported baseline body weight, this was used to calculate units/day. Where the RCTs did not report body weight, doses were converted to units/day using the average weight for second intensification people with type 2 diabetes in the baseline THIN data (87.6 kg, see table 20). As men and women were not modelled separately, the average weight for all people was used.

No adjustments to dosing were made to reflect changing body weight. Whilst this may slightly advantage insulin-based treatment options (as their costs did not increase over time), the 0.1 kg/year weight increase would add less than £1/year to insulin costs – with discounting applied the impact would be reduced over time. Similarly, insulin doses were not increased over time to reflect worsening HbA1c profiles. These are common assumptione in the published literature.

3.8.3 Drug unit costs

Drug unit costs were based on prices published in the July 2014 NHS Drug Tariff (see table 63) (Joint Formulary Committee 2014). For oral drugs, the cheapest pack sizes (based on total cost per mg) in the NHS Drug Tariff were used and it was assumed no combination tablets were used.

Liraglutide and insulin prices were not available in the NHS Drug Tariff so prices for these drugs were taken from The NHS Dictionary of Medicines and Devices (DMD). Insulins were costed using the weighted average of the various available cartridges, pre-filled pens and vials (Health and Social Care Information Centre (HSCIC) 2014b)although in reality costs for each variation were usually very close. NPH insulin was weighted by brand, using the weighted average units prescribed divided by the net ingredient cost. Brands used to cost for biphasic insulins are shown in table 63.

Table 63: Drug unit costs

Drug	Cost per unit	Units
Biphasic insulin aspart (NovoMix 70/30)	£0.01970	unit
Exenatide (daily)	£1.13733	dose[a]
Insulin degludec	£0.04800	unit
Insulin detemir	£0.02804	unit
Insulin glargine	£0.02778	unit
Insulin lispro mix 25 (Humalog Mix 25)	£0.02004	unit
Insulin lispro mix 50/50 (Humalog Mix 50)	£0.02030	unit
Linagliptin	£0.23757	mg
Liraglutide	£2.18000	mg
Metformin	£0.00004	mg
Nateglinide	£0.00257	mg
NPH insulin	£0.01381	unit
Pioglitazone	£0.00131	mg
Placebo	£0.00000	mg
Repaglinide	£0.03217	mg
Saxagliptin	£0.22571	mg
Sitagliptin	£0.01188	mg
Sulfonylurea	£0.00059	mg
Vildagliptin	£0.01134	mg

(a) Exenatide costed per dose as both strengths (5mcg and 10mcg) have the same unit cost

3.9 Drug consumables and staff time

In addition to drug costs, we included the resource use and costs of various consumables and staff time . We calculated consumable use per day and converted this to an annual cost. A full list of resource use by therapy is given in table 65 and unit costs are given in table 64.

We assumed that some treatment regimens require regular self-monitoring of blood glucose (SMBG) tests. The GDG gave advice on the average numbers of SMBG tests per day that would be used. Where a first or second intensification treatment option contained more than 1 treatment that required SMBG, we used the maximum (rather than additive) number of tests. On GDG advice, SMBG strips and lancets were assumed to be used once only. SMBG meters and lancet devices were assumed to have no cost to the NHS.

Rather than selecting the cost of particular brands, we costed SMBG lancets and test strips using the weighted average of prescribed usage by brand (Health and Social Care

Information Centre (HSCIC) 2014b). We noted that the prescription data were not specific to people with type 2 diabetes, but the GDG saw no reason that the brands used would differ between people with type 1 diabetes and people with type 2 diabetes. In this way, we estimated a cost of 29p per strip and 4p per lancet, giving a total cost of 33p per SMBG test (see table 64).

For injectable treatment options, we took the number of disposable needles used per day from the included RCTs. We assumed disposable needles would be used once and, like SMBG lancets and test strips, we costed these using the weighted average of prescribed usage by brand (Health and Social Care Information Centre (HSCIC) 2014b) (11p per needle, see table 64). Again, the GDG saw no reason that the brands used would differ between people with type 1 diabetes and people with type 2 diabetes.

The GDG assumed that people requiring sharps bins would use an average of 3 bins per year, at an average weighted cost of 85p per bin.

We assumed that people initiating injectable treatment options would require additional primary care consultations in the year they initiated insulin. The GDG advised that these consultations would be likely to be with an advanced level practice nurse (band 7), who cost £52/hour (Curtis 2014). For GLP-1 agonist treatment options, the GDG assumed 2 × 20 minutes appointments would be required to initiate and check usage. For insulin-based treatment options, the GDG assumed 1 × 40-minute appointment would be required followed by 7 × 20 minute appointments (based on an average of 6–8 follow-up appointments) to titrate insulin dosage. This gave a total cost for practice nurse initiation time of £35 for GLP-1 agonist treatment options and £156 for insulin-based treatment options (see table 64).

Insulin initiation costs were applied to the first year of insulin therapy. If, due to intolerance, a simulated person switched from a GLP-1 agonist treatment option or a different insulin-based treatment option to metformin-NPH insulin (see table 15), the model applied the insulin initiation costs for a second time. This could be seen as a slight limitation of the original health economic model that biased against GLP-1 agonist or insulin-based treatment options with high dropout rates, but people may still need primary care appointments in order to titrate their new treatment option.

For insulin initiation, the previous guideline (National Institute for Health and Care Excellence 2009) assumed a mixture of face-to-face and telephone appointments with hospital-based nurses, which gave a total staff time cost of £206 (adjusted to 2012 prices, (Curtis 2014)). The slightly lower cost adopted by this guideline may reflect changing patterns of care, with most people with type 2 diabetes now being cared for and likely to initiate insulin in primary rather than secondary care.

Table 64: Consumable and staff time unit costs

Resource	Unit Cost
Disposable Needle	£0.11
SMBG strip	£0.29
SMBG lancet	£0.04
Sharps bin	£0.85
GLP-1 agonist initiation (2*20 min band 7 practice nurse appointments)	£34.67
Insulin Initiation (1*40 min and 7*20 min band 7 practice nurse appointments)	£156.00

Table 65: Drug consumables and staff time resource usage assumptions

Therapy Level	Treatment	SMBG /Day	Needles /Day	Sharps bin	Nurse initiation
Initial	Metformin	0	0	No	No
	Pioglitazone	0.429	0	No	No
	Placebo	0	0	No	No
	Repaglinide	0	0	No	No
	Sitagliptin	0	0	No	No
	Sulfonylurea	0.429	0	No	No
	Vildagliptin	0	0	No	No
First intensification	Exenatide-metformin	0.429	2	Yes	GLP-1
	Linagliptin-metformin	0	0	No	No
	Liraglutide-metformin	0.429	1	Yes	GLP-1
	Metformin-pioglitazone	0.429	0	No	No
	Metformin-sitagliptin	0	0	No	No
	Metformin-sulfonylurea	0.429	0	No	No
	Metformin-vildagliptin	0	0	No	No
Second intensification	Biphasic insulin aspart-metformin	2	2	Yes	Yes
	Biphasic insulin aspart-metformin-sulfonylurea	2	2	Yes	Yes
	Biphasic insulin aspart-repaglinide	2	1	Yes	Yes
	Exenatide-metformin-sulfonylurea	0.429	2	Yes	GLP-1
	Insulin degludec/aspart mix-metformin	2	1	Yes	Yes
	Insulin degludec-metformin	2	1	Yes	Yes
	Insulin detemir-metformin	2	1	Yes	Yes
	Insulin glargine-metformin	2	1	Yes	Yes
	Insulin glargine-metformin-sulfonylurea	2	1	Yes	Yes
	Insulin glargine-sulfonylurea	2	1	Yes	Yes
	Insulin lispro mix 50 and mix 25	2	2	Yes	Yes
	Insulin lispro mix 50/50-metformin	2	3	Yes	Yes
	Liraglutide-metformin-sulfonylurea	0.429	1	Yes	GLP-1
	Metformin-NPH insulin	2	1	Yes	Yes
	Metformin-NPH insulin-repaglinide	2	1	Yes	Yes
	Metformin-NPH insulin-sulfonylurea	2	1	Yes	Yes
	Metformin-pioglitazone-sulfonylurea	0.429	0	No	No
	Metformin-sitagliptin-sulfonylurea	0.429	0	No	No
	NPH insulin	2	2	Yes	Yes
	NPH insulin-sulfonylurea	2	1	Yes	Yes

(a) 0.429 SMBG tests/day equivalent to 3 SMBG tests/week
(b) Nurse initiation resource use for GLP-1 agonist treatment options lower than for insulin based treatment options

A considerable proportion of people with type 2 diabetes will struggle to or be unable to administer their own injections. The GDG discussed including a cost for district nurse administration for injectable treatment options for some people. However, no evidence could be found to indicate what proportion of people with type 2 diabetes on injectable treatment options require district nurse administration, or to indicate how much district nurse resource would be required. Even if 3% of people with type 2 diabetes on injectable treatment options were assumed to require 45 minutes of district nurse input each day, the requirement for daily input meant district nurse input had the potential to dwarf the other drug costs. The

GDG felt that treatment intensification decisions for this subgroup of the type 2 diabetes population would be different. The additional cost of district nurse administration should be borne in mind for this population, along with considerations of the impact of lower HbA1c targets and more intensive regimes on such people.

3.9.1 Weighted average drug dose and annual treatment costs

Drug unit costs were combined with weighted average doses specific to each treatment option to produce weighted average daily doses and daily drug costs. Annual treatment costs combined drug costs, consumables and staff time. Costs were calculated separately for initiation year (year 1) and subsequent years (year 2 onwards). Doses and costs are summarised by therapy level in table 66, table 67 and table 68.

Table 66: Weighted average daily doses from included RCTs and annual treatment costs – initial therapy

	Daily dose (mg)		Daily drug cost		Annual treatment cost	
Treatment	Year 1	Year 2 onwards	Year 1	Year 2 onwards	Year 1	Year 2 onwards
Metformin	1663.6	1751.5	£0.06	£0.07	£22.56	£24.03
Pioglitazone	39.0	43.4	£0.05	£0.06	£70.83	£72.93
Placebo	0	0	£0.00	£0.00	£0.00	£0.00
Repaglinide	3.8	4.0	£0.12	£0.13	£44.90	£46.48
Sitagliptin	84.3	84.3	£1.00	£1.00	£365.55	£365.55
Sulfonylurea	148.4	158.9	£0.09	£0.09	£84.23	£86.48
Vildagliptin	93.6	93.6	£1.06	£1.06	£387.97	£387.97

(a) Annual treatment cost includes drugs, consumables and initiation staff time

Table 67: Weighted average daily doses from included RCTs and annual treatment costs – first intensification of therapy

Treatment	Daily Dose (mg unless stated)		Daily Drug Cost		Annual Treatment Cost	
	Year 1	Year 2 onwards	Year 1	Year 2 onwards	Year 1	Year 2 onwards
Exenatide-metformin			£2.35	£2.35	£1031.15	£995.48
Exenatide	2.0 doses	2.0 doses				
Metformin	2000.0	2000.0				
Linagliptin-metformin			£1.24	£1.24	£453.65	£453.65
Linagliptin	5.0	5.0				
Metformin	1500.0	1500.0				
Liraglutide-metformin			£2.92	£2.94	£1196.24	£1168.54
Liraglutide	1.0	1.3				
Metformin	2000.0	2000.0				
Metformin-pioglitazone			£0.11	£0.11	£91.42	£93.29
Metformin	1822.6	1822.6				
Pioglitazone	24.7	35.6				
Metformin-sitagliptin			£1.26	£1.26	£459.28	£459.28
Metformin	1926.3	1926.3				
Sitagliptin	100.0	100.0				
Metformin-sulfonylurea			£0.14	£0.15	£104.32	£107.64
Metformin	1771.6	1858.6				
Sulfonylurea	78.5	143.6				
Metformin-vildagliptin			£1.20	£1.20	£439.71	£439.71
Metformin	1926.3	1926.3				
Vildagliptin	100	100.0				

(a) Annual treatment cost includes drugs, consumables and initiation staff time
(b) Exenatide costed per dose as both strengths (5mcg and 10mcg) have the same unit cost

Table 68: Weighted average daily doses from included RCTs and annual treatment costs – second intensification of therapy

	Daily Dose (mg unless stated)		Daily Drug Cost		Annual Treatment Cost	
Treatment	**Year 1**	**Year 2 onwards**	**Year 1**	**Year 2 onwards**	**Year 1**	**Year 2 onwards**
Biphasic insulin aspart-metformin			£0.91	£1.08	£816.77	£724.47
Biphasic insulin aspart	42.5 units	51.4 units				
Metformin	1908.3	1908.3				
Biphasic insulin aspart-metformin-sulfonylurea			£0.67	£0.78	£732.16	£615.23
Biphasic insulin aspart	25.8 units	31.2 units				
Metformin	2000.0	2000.0				
Sulfonylurea	160.0	160.0				
Biphasic insulin aspart-repaglinide			£0.50	£0.72	£628.21	£552.26
Biphasic insulin aspart	17.1 units	28.3 units				
Repaglinide	5.2	5.2				
Exenatide-metformin-sulfonylurea			£2.35	£2.44	£1032.63	£1029.92
Exenatide	1.9 doses	2.0 doses				
Metformin	2000.0	2000.0				
Sulfonylurea	160.0	160.0				
Insulin degludec/aspart mix-metformin			£0.64	£0.70	£676.51	£544.60
Insulin lispro mix 50/50	27.1 units	30.2 units	Degludec/aspart mix was a proof of concept formulation so cost unknown. Two strengths were used, so costed as lispro mix. Note that degludec is usually more expensive than lispro			
Insulin lispro mix 75/25	28.9 units	32.3 units				
Metformin	2000.0	2000.0				
Insulin degludec-metformin			£1.88	£2.09	£1129.39	£1050.82
Insulin degludec	37.6 units	42.0 units				
Metformin	2000.0	2000.0				
Insulin detemir-metformin			£1.35	£1.69	£938.50	£904.42
Insulin detemir	45.7 units	57.6 units				
Metformin	2000.0	2000.0				
Insulin glargine-metformin			£1.25	£1.42	£899.51	£806.84
Insulin glargine	42.3 units	48.5 units				
Metformin	1993.1	1993.1				

Treatment	Daily Dose (mg unless stated)		Daily Drug Cost		Annual Treatment Cost	
	Year 1	Year 2 onwards	Year 1	Year 2 onwards	Year 1	Year 2 onwards
Insulin glargine-metformin-sulfonylurea			£0.76	£0.87	£722.13	£604.57
Insulin glargine	21.7 units	25.5 units				
Metformin	1972.5	1972.5				
Sulfonylurea	148.2	148.2				
Insulin glargine-sulfonylurea			£0.94	£1.06	£788.75	£673.30
Insulin glargine	31.2 units	35.2 units				
Sulfonylurea	131.1	131.1				
Insulin lispro mix 50 and mix 25			£0.78	£0.90	£771.43	£656.67
Insulin lispro mix 50/50	38.5 units	44.1 units		Mix 50 & 25 same unit cost, only 50 costs shown		
Insulin lispro mix 50/50-metformin			£1.36	£1.40	£1024.52	£882.02
Insulin lispro mix 50/50	63.5 units	65.3 units				
Metformin	2000.0	2000.0				
Liraglutide-metformin-sulfonylurea			£3.98	£4.08	£1583.30	£1585.39
Liraglutide	1.8	1.8				
Metformin	2000.0	2000.0				
Sulfonylurea	136.0	136.0				
Metformin-NPH insulin			£0.74	£0.87	£712.74	£606.27
Metformin	2234.2	2252.0				
NPH insulin	47.4 units	57.2 units				
Metformin-NPH insulin-repaglinide			£0.64	£0.70	£679.25	£543.14
Metformin	1700.0	1700.0				
NPH insulin	17.5 units	18.2 units				
Repaglinide	10.6	12.0				
Metformin-NPH insulin-sulfonylurea			£0.52	£0.56	£634.03	£491.47
Metformin	2079.5	2079.5				
NPH insulin	28.7 units	29.9 units				
Sulfonylurea	160.0	160.0				

Treatment	Daily Dose (mg unless stated)		Daily Drug Cost		Annual Treatment Cost	
	Year 1	Year 2 onwards	Year 1	Year 2 onwards	Year 1	Year 2 onwards
Metformin-pioglitazone-sulfonylurea			£0.23	£0.23	£135.74	£137.90
Metformin	1500.0	1500.0				
Pioglitazone	38.1	45.0				
Sulfonylurea	200.0	200.0				
Metformin-sitagliptin-sulfonylurea			£1.40	£1.40	£564.67	£564.67
Metformin	1717.0	1717.0				
Sitagliptin	100.0	100.0				
Sulfonylurea	260.0	260.0				
NPH insulin			£0.66	£0.87	£725.78	£647.00
NPH insulin	78.3 units	100.4 units				
NPH insulin-sulfonylurea			£0.52	£0.57	£632.06	£497.28
NPH insulin	19.6 units	21.0 units				
Sulfonylurea	162.0	162.0				

(a) Annual treatment cost includes drugs, consumables and initiation staff time
(b) Exenatide costed per dose as both strengths (5mcg and 10mcg) have the same unit cost

3.9.2 Treatment dropouts due to intolerance resource use and costs

As outlined in section 3.2.5, the original health economic model allowed people to switch treatments (within a therapy level) due to intolerance. We assumed that switching treatments would require 1 × 12-minute GP appointment, at a cost of £45 each (Curtis 2014).

3.9.3 Weight-change costs

Treatment-related weight-change was assumed to have no resource use or cost impact to the NHS.

3.9.4 Hypoglycaemia resource use and costs

The cost to the NHS of hypoglycaemic events is uncertain. Not all severities of hypoglycaemic episode are treated in the same way, with people self-treating, receiving assistance from friends and only occasionally using NHS services.

Clearly, resource use differs by the severity of hypoglycaemic episodes. Symptomatic episodes – defined by the GDG as where the person was able to treat themselves – were assumed to incur no NHS resource use. Severe episodes – defined by the GDG as those where the person requires external assistance – would sometimes be treated by friends and family and only sometimes by NHS services (primary care, ambulance services and A&E, secondary care). Whilst the GDG were most interested in rates of all hypoglycaemic episodes (see 3.2.7), for resource use and cost purposes it was necessary to determine what proportion of all hypoglycaemic episodes were severe, and what proportion of severe episodes incurred NHS resource use and cost.

We largely based resource use and unit costs for severe hypoglycaemic episodes on Hammer et al. (2009). The paper included a UK sample of non-randomly selected people with type 2 diabetes on insulin-based treatment options (Hammer et al. 2009). Of 147 people, 19 reported having at least 1 severe hypoglycaemic episode in the previous 1 year (giving a severe hypoglycaemia rate not dissimilar to that taken from Donnelly et al. (2005) in our model). 53% of the 19 people reporting a severe hypoglycaemic episode were treated by the NHS. We combined this figure with weighted estimated costs of managing severe hypoglycaemic events in the community and hospital (weighted by the percentages of severe hypoglycaemic events in each setting, see table 69) and inflated to 2012-13 prices to estimate the NHS cost of a severe hypoglycaemic event of £380. The GDG felt such a cost was not unrealistic.

Table 69: Weighting of NHS costs of severe hypoglycaemic events

Severe hypoglycaemic events	NHS cost per severe hypoglycaemic event	Percentage of severe hypoglycaemic events
Managed in the community	£231	35%
Managed in hospital	£862	65%

(a) Source: Hammer et al. (2009)

A recent NICE technology appraisal questioned the applicability of the industry-sponsored Hammer et al. (2009) paper (National Institute for Health and Care Excellence 2013). However, the technology appraisal Evidence Review Group did not suggest an alternative source, but rather questioned the assumption that around 50% of people experiencing a severe hypoglycaemic event would be treated by the NHS. The GDG were happy to assume that 50% of events were treated by the NHS.

The previous guideline (National Institute for Health and Care Excellence 2009) used an earlier UK costing paper (Leese et al. 2003) that produced a cost per severe hypoglycaemic episode of £431 (converted to 2012 prices) (Curtis 2014). The previous guideline also chose

to assume a lower proportion of people were treated by the NHS (20%) so their overall cost per hypoglycaemic episode was £86 (2012 prices). Having discussed these estimates, the GDG felt that a cost per severe hypoglycaemic event of £380 was more realistic and were happy to use this figure in the original health model.

3.10 Utilities

We took our estimate of baseline utility for a person with type 2 diabetes from the UKPDS RCT (Clarke et al. 2002). The figure of 0.785 matched the requirement of the NICE reference case (National Institute for Health and Care Excellence 2012b), but is lower than the baseline utility used in some type 2 diabetes models and CUAs.

Along with other potential sources, the UKPDS baseline utility has a number of limitations. The investigators report an average baseline utility that is based on a male with type 2 diabetes aged 59 years – ideally for this model, a slightly different baseline utility would be used for each intensification, based on age and both genders. Also, we could not reduce baseline utility as the age of simulated individuals advances, as it is not possible to specify time-dependent utilities in UKPDS OM1. This will slightly bias in favour treatments that extend life years but, given the impact of discounting and the anticipated tiny differences between treatments in life expectation, any bias is likely to be negligible.

3.10.1 Long-term outcome utility decrements

As for costs (see 3.8.1), we took long-term outcome utility decrements from UKPDS publications (Clarke et al. 2002), in order to exactly match the complication definitions used the UKPDS model (see table 70). Again, renal failure was a necessary exception, for which we took our utility decrement from source recommended for UKPDS OM1 (Kiberd and Jindal 1995). Long-term outcome utility decrements were treated as additive across multiple complications.

Table 70: Long-term outcome utility decrements

Long-term outcome	Annual utility decrement
IHD	-0.090
MI	-0.055
CHF	-0.108
Stroke	-0.164
Amputation	-0.280
Blindness	-0.074
Renal failure	-0.263

(a) IHD = ischaemic heart disease, MI = myocardial infarction, CHF = congestive heart failure, Renal failure = end stage renal failure

We only included other utility decrements if they could be assumed not to have been captured in the UKPDS RCT utilities.

3.10.2 Treatment dropouts due to intolerance utility decrements

The GDG felt that applying a utility decrement when people switched treatments within a therapy level due to intolerance was appropriate both to reflect the adverse effects that would lead to treatment dropouts due to intolerance and also to avoid incentivising switching treatments.

It was felt that a utility decrement associated with nausea would be a reasonable proxy for the array of treatment-related adverse events that may cause people to switch treatments.

Given that people would be likely to experience adverse events within the early weeks of treatment, the model applied utility decrements for treatment dropouts to the first year of treatment only. The GDG chose to apply the utility decrement associated with nausea for 6 weeks. This assumption was less than used the previous guideline (National Institute for Health and Care Excellence 2009) or published CUAs where nausea is a key adverse event (Beaudet et al. 2011; Ray et al. 2007). The annual utility decrement applied was −0.005 (Matza et al. 2007); however, we note that, in this industry-sponsored study, it was unclear what treatment options people were taking (particularly how many were taking GLP-1 agonist treatment options).

3.10.3 Weight-change utility decrements

For an estimate of the health-related quality of life impact associated with treatment-related weight-change, we selected the utility decrement reported by Bagust and Beale (2005). The same utility decrement has been used in the previous guideline (National Institute for Health and Care Excellence 2009) and recent technology appraisals (National Institute for Health and Care Excellence 2012a; National Institute for Health and Care Excellence 2013; National Institute for Health and Care Excellence 2014). The paper was a prospective, type 2-specific (but not UK-based) analysis of the relationship between utility and type 2 diabetes complications, including weight-change (Bagust and Beale 2005). Bagust and Beale (2005) produced a annual utility decrement of −0.0061 per unit of BMI greater than 25 kg/m^2. The mean BMI in Bagust and Beale (ref) was 28.7 kg/m^2.

Whilst Bagust and Beale (2005) applied a utility decrement of −0.0061 per unit of BMI greater than 25 kg/m^2, the original health economic model used a BMI of 27.7 kg/m^2 as the centring BMI. This was the BMI value of the average person in the UKPDS RCT (Stratton et al. 2000). In effect, then, we assume that (27.7−25) × −0.0061 = −0.0165 of the baseline utility associated with type 2 diabetes is ascribable to the amount of excess BMI seen, on average, in the UKPDS cohort. However, this is mathematically identical to centring utility calculations around a value of 27.7 kg/m^2 rather than 25 kg/mg^2, so this was how we applied the effect in the model.

The recent dapgliflozen technology appraisal (National Institute for Health and Care Excellence 2013) advised against using higher utility values, such as those from Matza et al. (2007). A recent systematic review of utility values used type 2 diabetes modelling noted that the utility decrement from Bagust and Beale (2005) was amongst the lowest published values and was the methodologically preferred value (Beaudet et al. 2014). An earlier systematic review suggested that Soltoft et al. (2009) may provide alternative (and lower) utility decrements associated with weight-changes (Doyle et al. 2012; Soltoft et al. 2009). Soltoft et al. (2009) was a large retrospective analysis of survey data, but the utility decrements calculated were not specific to type 2 diabetes. Hence, we preferred the utility decrements associated with weight-change from Bagust and Beale (2005).

The impact of treatment-related weight-change utility decrements varied according to the weight profiles modelled (see 3.2.6).

Because UKPDS OM1 requires both height and weight to be specified for each generated person, conversion from weight-change to BMI was calculated at an individual level.

3.10.4 Hypoglycaemia-related utility decrements

As rates of hypoglycaemia were related only to the treatment option and not to other baseline characteristics, risk factors or complications, the original model did not feed hypoglycaemic episode utility decrements through UKPDS OM1.

We used the same source of hypoglycaemic episode utility decrement (Currie et al. 2006) as the previous type 2 diabetes guidelines (National Institute for Health and Care Excellence 2008; National Institute for Health and Care Excellence 2009). The previous guideline in particular noted weaknesses of Currie et al. (2006) that included low response rate, potential recall bias and industry sponsorship. However, a strength of Currie et al. (2006) was the multivariate analysis undertaken.

The original health economic analysis models utility decrements associated with symptomatic and severe hypoglycaemic episodes slightly differently. This is a result of the way the utility decrements applied were calculated.

The model calculated utility decrements for symptomatic hypoglycaemic episodes using a log-transformation of the number of hypos, in reflection of the methods used by Currie et al. (2006). This has the impact that the marginal utility loss of each additional symptomatic hypoglycaemic episode will be smaller than for the previous episode. For example, the impact of having 10 as opposed to 5 episodes per year is much greater than the impact of having 50 as opposed to 45 episodes per year. In previous CUAs, the utility decrement has been applied equally to each symptomatic hypoglycaemic episode. Applying it as a log-transformed variable was not only a better reflection of the underlying utility evidence, but also seemed more intuitively reasonable to the GDG.

To calculate the number of symptomatic hypoglycaemic episodes, the probability density function of a Poisson distribution with a given rate of events was summed for 0 to 500 symptomatic hypoglycaemic episodes. 500 symptomatic hypoglycaemic episodes per year is equivalent to more than 1 episode per day and was chosen to be a conservatively high cut-off which would be unlikely to occur in reality or be generated probabilistically by the original health economic model. Also, as the log-transformation is applied, the marginal impact of the 501st symptomatic hypoglycaemic episodes will be negligible.

Algebraically, the annual utility impact of symptomatic hypos is estimated as

$$u_{symp} = \sum_{i=1}^{500} \mathrm{P}(\lambda, i) \ln(i)\, d_{symp} \qquad \textbf{(4)}$$

where P(λ,*i*) is the probability mass function of the Poisson distribution for an event-rate of symptomatic hypos of λ evaluated at *i* (i.e. the probability that a process with event-rate λ would result in precisely *i* events) and d_{symp} is the utility decrement ascribable to each symptomatic hypo (when that count is log-transformed).

Making the Poisson function in **(4)** explicit gives

$$u_{symp} = \sum_{i=1}^{500} \frac{\lambda^i e^{-\lambda}}{i!} \ln(i)\, d_{symp} \qquad \textbf{(5)}$$

For high values of *i*, the calculation of Poisson probabilities becomes computationally burdensome, and a normal approximation is very commonly used. The POISSON.DIST() function in Excel was used for this calculation, which does not appear to use a normal approximation over the range of values tested.

Using the log-transformation could appear to attach no utility decrement to a treatment option with a rate of 1 symptomatic hypoglycaemic episode per year. However, as the utility decrements were modelled using the probability density function, a treatment with a

symptomatic hypoglycaemia rate of exactly 1 symptomatic hypoglycaemic episode per year would be not have the same utility decrement as a treatment year with no symptomatic hypoglycaemic episodes, as the rate of 1 is the mean of the distribution rather than a single value.

A slightly different approach was necessary for severe hypoglycaemic episodes, as the utility decrements are handled differently in Currie et al. (2006). Severe hypoglycaemic episodes were modelled as binary events – a person reporting at least 1 severe hypoglycaemic event in a 3-month period versus reporting 0 severe hypoglycaemic events in the period. As the original health economic model has annual cycles, this was modelled using a binomial distribution.

The annual utility impact of severe hypos is estimated as

$$u_{sev} = \sum_{i=1}^{4} \mathrm{B}(i, 4, p) \frac{d_{sev} i}{4} \quad \textbf{(6)}$$

where B(*i,4,p*) is the probability mass function of the binomial distribution for 4 independent 'trials', each of which yields 'success' with probability *p*, evaluated at *i* (i.e. the probability that a sequence of 4 discrete periods, during each of which the probability that 1 or more event will occur is *p*, would result in *i* periods during which the event occurred at least once). In the case in hand, this provides an estimate of the probability that an individual would have 1, 2, 3 or 4 quarter-years with 1 or more severe hypoglycaemic episode, given an underlying probability of the event. These probabilities are then multiplied by the utility loss that would be expected for each of the 4 cases and summed.

Because the occurrence of severe hypos is estimated as an annual rate, it is necessary to transform this into a quarterly probability before applying this calculation, i.e.

$$p = 1 - e^{-\lambda \frac{1}{4}} \quad \textbf{(7)}$$

Making the binomial function in **(6)** explicit, we have

$$u_{sev} = \sum_{i=1}^{4} \frac{4!}{i!\,(4-i)!} p^{i} (1-p)^{4-i} \frac{d_{sev} i}{4} \quad \textbf{(8)}$$

The utility decrement for severe hypoglycaemic episodes given in Currie et al. (2006) is −0.047. In line with the ERG report on the recent technology appraisal for dapagliflozen (National Institute for Health and Care Excellence 2013), this was viewed as a 3-monthly figure and was divided by 4 to give an annual figure (−0.012) when applied. Previous CUAs appear to have assumed that, if a person has a severe hypoglycaemic episode in a given quarter, the person does not have another episode in the rest of that year. Thus, unlike previous approaches, the original health economic model allowed for the differing probabilities of having quarter-on-quarter severe hypos in a given year.

The GDG gave nocturnal hypoglycaemic episodes the lowest priority (see 3.5.4.4) and did not wish to model potential differences in nocturnal hypoglycaemic episodes between treatments. According, we did not include a utility decrement related to nocturnal hypoglycaemic episodes in particular (though these will have been included in rates of 'all'

episodes) and we took the utility decrements from the Currie et al. (2006) multivariate model that did not include nocturnal hypoglycaemic episodes.

The GDG also chose not to apply a utility decrement related to the fear of hypoglycaemia. The previous guideline (National Institute for Health and Care Excellence 2009) chose to assume a 0.01 utility gain per year from reduced fear associated with severe hypoglycaemic episode.

People with type 2 diabetes in Currie et al. (2006) reported higher rates of symptomatic hypoglycaemic episodes (24 episodes per year) than used as baseline rates in this model (15 per year) (Donnelly et al. 2005). This could be due to a number of factors, including positive response bias (people experiencing hypoglycaemic episodes being more likely to respond), unknown insulin brand usage or unknown treatment options. Currie et al. (2006) and Donnelly et al. (2005) have similar definitions of hypoglycaemia, but Donnelly et al. (2005) encouraged people to use SMBG. This could have led to a reduction in reported hypoglycaemic episodes as people may have not reported episodes which they thought were hypoglycaemia but their test did not confirm low blood sugar. A number of treatments in our model had symptomatic hypoglycaemic episode rates as high or higher than 24 episodes per year, including biphasic insulin aspart with metformin.

It is notable and unusual that Currie et al. (2006) report virtually the same rates of symptomatic hypoglycaemic episodes for people with type 2 diabetes on oral agents (24.1 episodes per year) as those on insulin (24.3 episodes per year). However, the overall proportion of severe hypoglycaemic episodes (2.1%) is very similar to that used in the original health economic model from Leese et al. (2003).

A recent systematic review of utility values used in type 2 diabetes modelling noted that the utility decrements for hypoglycaemic episodes from Currie et al. (2006) were the smallest utility decrements published (Beaudet et al. 2014).

It is not apparent that the Currie et al. (2006) has been correctly applied in previous guidelines and publications. We believe that the way our model applies both symptomatic and severe hypoglycaemic episode utility decrements represents a better interpretation of the underlying utility study by Currie et al. (2006).

3.11 Sensitivity analyses

3.11.1 Probabilistic sensitivity analyses (PSA)

For each therapy level, 1000 PSA iterations were run in order to evaluate and combine all sources of uncertainty within the original health economic model (see table 12). We chose to perform 1000 PSA iterations both because it is a common standard for PSAs and also because there are 1000 bootstrapped coefficient values available in UKPDS OM1. Bootstrapped coefficient values represent parameter uncertainty from the use of estimated parameters within the UKPDS risk and outcome equations. The investigators refitted the equations to datasets that were randomly resampled with replacement from the original data, and the 1000 resulting sets of coefficients were recorded (Clarke et al. 2004). In our PSA, each iteration used a single different set of bootstrapped coefficients (see 3.2.2).

In addition to UKPDS OM1 risk and long-term outcome equations, the PSA varied all other parameters that were used as inputs to – or for calculations consequent upon – UKPDS OM1 modelling. This included all efficacy and safety parameters (see 3.6), baseline hypoglycaemia rates, daily drug and consumables costs, UKPDS OM1 long-term outcome costs, severe hypoglycaemia costs, treatment dropout costs and all utility and disutility values (see figure 2).

Distributions and parameters used to vary parameter values are shown in Table 82. For a number of parameters, standard errors were not available and were assumed to be 20% of the parameter. The published blindness utility decrement confidence interval from the tobit model (−0.252, −0.124) did not contain the utility decrement point estimate (−0.074) (Clarke et al. 2004). Therefore, we used the published confidence interval from the CLAD model (−0.088, −0.003) instead to calculate the standard error used in the PSA.

For each simulated person in each PSA iteration, the same model parameters were used and, to ensure parameter uncertainty remained appropriately nested within the PSA iteration, a single UKPDS OM1 bootstrap was used. A different set of model parameters, 50,000 new people and a different UKPDS bootstrap was used for each subsequent PSA run.

The previous guideline did not produce a PSA, as the authors were not confident they were able to characterise the uncertainty around treatment effects and align different aspects of uncertainty. However, the modular approach of the original health economic model (see figure 2) allowed the various sources of uncertainty to be adequately modelled and combined.

3.11.2 One-way sensitivity analyses

Due to the nature and structure of the original health economic model (see 3.2), it was not possible to run full 1-way sensitivity analyses covering every parameter. However, a number of structural assumptions were tested and a number of parameters from the outer parameter set were varied.

One-way sensitivity analyses were stochastic model runs using 50,000 people and 1000 UKPDS OM1 loops. Note that, for these analyses, we raised the number of ‘inner’ loops from 100 to 1000. This is because, whereas we were confident that any variation introduced by running 100 UKPDS OM1 loops would be ‘smoothed’ across 1000 ‘outer’ loops, we wanted to minimise the chance of introducing excess random error into these single analyses. This had additional computational burden; however, we had enough capacity to cope with this for a limted number of sensitivity analyses.

We acknowledge that, for sensitivity analyses that only impact 1 of costs or QALYs, the costs and QALYs for each treatment option will not exactly match those in the base-case results (which were based on the means of 1000 PSA iterations). However, the 1-way sensitivity analyses results were sufficient to give an indication of model dynamics and the impact of key assumptions on the results.

3.11.2.1 Use of year 2 HbA1c and weight treatment effect data

For initial therapy and first intensification, the base-case model used HbA1c and weight treatment effect data from NMAs at 1 year. However, HbA1c and weight treatment effect data were also available for some treatments at 2 years. Because of sparser reporting at second intensification, 2-year HbA1c and weight treatment effects were not available.

Year-2 treatment effect data were only available for a subset of treatments – this included some treatments where year-1 data were not available and, therefore, we were not able to model these treatments in the base-case analysis. Given this, year-2 treatment effect data were analysed in 2 ways (see table 71).

In scenario 1, year-2 treatment-effect data were used wherever they were available (in addition to year-1 data). In scenario 2, year-2 treatment-effect data were only used where no year-1 treatment data were available for a particular treatment. If year-1 data were available, then year-2 data were extrapolated (using the UKPDS OM1 time path equation for HbA1c (Clarke et al. 2004)) rather than being taken from the clinical networks. In both cases, for treatments where no year-1 data were available, they were estimated using linear

interpolation between baseline and year-2 data (that is, half of the year-2 change was applied in year 1 and the other half was applied in year 2).

Using year-2 data enabled 3 additional treatments to be modelled at first intensification: metformin-nateglinide, metformin-saxagliptin and pioglitazone-sulfonylurea. Year-2 treatment-effect data for initial therapy and first intensification treatment options are shown in table 76 and table 77, respectively. Year-2 data represent the total treatment effect at year 2, not the change from year 1 to year 2.

Table 71: Comparison of data used in 2-year data sensitivity analyses

Data availability for given treatment	Scenario 1: use year-2 data wherever available			Scenario 2: use year-2 data only where year-1 data unavailable		
	Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
Year 1 available Year 2 available	Year 1	Year 2	Extrapolated from year 2	Year 1	Extrapolated from year 1 (year 2 not used)	
Year 1 unavailable Year 2 available	Interpolated from year 2	Year 2	Extrapolated from year 2	Interpolated from year 2	Year 2	Extrapolated from year 2
Year 1 available Year 2 unavailable	Year 1	Extrapolated from year 1		Year 1	Extrapolated from year 1	

Table 72: Safety and efficacy data inputs for 2-year data sensitivity analysis – initial therapy – HbA1c at 2 years

			Absolute change (%)			Relative effect (%)					
			Metformin			Acarbose	Pioglitazone	Placebo	Sitagliptin	Sulfonylurea	Vildagliptin
			Mean	Pred[a]	Beta[b]						
Mean			-1.049	n/a	n/a	-0.171	-0.983	0.099	0.001	-0.694	-0.502
SD			0.071	-	-	0.230	0.215	0.203	0.125	0.190	0.144
Correlation matrix											
Absolute change (%)	Metformin	Mean	1.000	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-
		Beta	-	-	1.000	-	-	-	-	-	-
Relative effect (%)	Acarbose		-	-	-	1.000	-	-	-	-	-
	Pioglitazone		-	-	-	0.413	1.000	-	-	-	-
	Placebo		-	-	-	0.880	0.475	1.000	-	-	-
	Sitagliptin		-	-	-	0.008	0.005	0.001	1.000	-	-
	Sulfonylurea		-	-	-	0.474	0.883	0.540	-0.002	1.000	-
	Vildagliptin		-	-	-	0.634	0.667	0.716	0.006	0.755	1.000

(a) Fixed-effects model preferred
(b) Unadjusted model preferred

Table 73: Safety and efficacy data inputs for 2-year data sensitivity analysis – initial therapy – weight at 2 years

			Absolute change (kg)		Relative effect (kg)				
			Metformin		Pioglitazone	Placebo	Sitagliptin	Sulfonylurea	Vildagliptin
			Mean	Pred[a]					
Mean			-2.039	n/a	3.477	3.764	1.272	3.773	2.978
SD			0.281	-	2.055	0.784	0.832	0.474	0.469
			Correlation matrix						
Absolute change (kg)	Metformin	Mean	1.000	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-
Relative effect (%)	Pioglitazone		-	-	1.000	-	-	-	-
	Placebo		-	-	0.116	1.000	-	-	-
	Sitagliptin		-	-	0.008	0.016	1.000	-	-
	Sulfonylurea		-	-	0.239	0.488	0.001	1.000	-
	Vildagliptin		-	-	0.198	0.586	-0.005	0.835	1.000

(a) Fixed-effects model preferred

Table 74: Safety and efficacy data inputs for 2-year data sensitivity analysis – first intensification – HbA1c at 2 years

			Absolute change (%)			Relative effect (%)					
			Metformin-Sulfonylurea			Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Pioglitazone-Sulfonylurea
			Mean	Pred[a]	Beta						
Mean			-0.557	n/a	-0.169	0.070	-0.034	-0.119	-0.060	-0.030	0.127
SD			0.020	-	0.035	0.042	0.115	0.074	0.058	0.067	0.121
Correlation matrix											
Absolute change (%)	Metformin	Mean	1.000	-	-	-	-	-	-	-	-
		Pred	-	1.000	-	-	-	-	-	-	-
		Beta	-0.347	-	1.000	-	-	-	-	-	-
Relative effect (%)	Linagliptin-Metformin		-	-	-	1.000	-	-	-	-	-
	Liraglutide-Metformin		-	-	-	-0.009	1.000	-	-	-	-
	Metformin-Pioglitazone		-	-	-	0.025	0.005	1.000	-	-	-
	Metformin-Saxagliptin		-	-	-	-0.013	0.015	0.006	1.000	-	-
	Metformin-Sitagliptin		-	-	-	0.033	-0.007	0.015	0.011	1.000	-
	Pioglitazone-Sulfonylurea		-	-	-	-0.015	0.000	-0.019	0.010	0.009	1.000

(a) Fixed-effects model preferred

Table 75: Safety and efficacy data inputs for 2-year data sensitivity analysis – first intensification – weight at 2 years

			Absolute change (kg)		Relative effect (kg)							
			Metformin-Sulfonylurea		Linagliptin-Metformin	Liraglutide-Metformin	Metformin-Nateglinide	Metformin-Pioglitazone	Metformin-Saxagliptin	Metformin-Sitagliptin	Metformin-Vildagliptin	Pioglitazone-Sulfonylurea
			Mean	Pred[a]								
Mean			0.896	n/a	-3.037	-3.310	-1.198	1.203	-2.798	-2.303	-1.497	4.910
SD			0.071	-	0.311	0.354	0.627	0.396	0.282	0.512	0.144	0.363
Correlation matrix												
Absolute change (kg)	Metformin	Mean	1.000	-	-	-	-	-	–			
		Pred	-	1.000	-	-	-	-	–			
Relative effect (%)	Linagliptin-Metformin		-	-	1.000	-	-	-	-	-	-	-
	Liraglutide-Metformin		-	-	-0.004	1.000	-	-	-	-	-	-
	Metformin-Nateglinide		-	-	-0.005	-0.002	1.000	-	-	-	-	-
	Metformin-Pioglitazone		-	-	0.009	0.017	0.002	1.000	-	-	-	-
	Metformin-Saxagliptin		-	-	-0.015	0.002	0.017	0.016	1.000	-	-	-
	Metformin-Sitagliptin		-	-	0.012	-0.007	0.011	0.002	-0.013	1.000	-	-
	Metformin-Vildagliptin		-	-	0.016	-0.005	-0.009	-0.011	0.019	0.011	1.000	-
	Pioglitazone-Sulfonylurea		-	-	0.007	0.001	-0.003	0.010	0.015	-0.000	-0.016	1.000

(a) Fixed-effects model preferred

Table 76: Year 2 absolute treatment effects modelled - initial therapy

Treatment	HbA1c[a]		Weight	
	Year 1	Year 2	Year 1	Year2
Metformin	-0.789	-1.049	-2.101	-2.039
Pioglitazone	-0.750	-2.033	+1.357	+1.438
Placebo	+0.050	-0.951	+0.391	+1.725
Repaglinide	-0.834	Not available	+1.091	Not available
Sitagliptin	-0.626	-1.048	-0.263	-0.767
Sulfonylurea	-0.636	-1.744	+1.491	+1.734
Vildagliptin	-0.332	-1.551	+0.095	+0.939

(a) HbA1c reductions based on an individual with baseline Hba1c equal to 7.5%

Table 77: Year 2 absolute treatment effects modelled – first intensification

Treatment	HbA1c[a]		Weight	
	Year 1	Year 2	Year 1	Year 2
Exenatide-metformin	-0.466	Not available	-2.848	Not available
Linagliptin-metformin	-0.563	-0.487	-1.246	-2.141
Liraglutide-metformin	-0.809	-0.592	-3.090	-2.413
Metformin-nateglinide[b]	-0.901	Not available	Not available	-0.302
Metformin-pioglitazone	-0.704	-0.676	+1.907	+2.100
Metformin-saxagliptin[b]	-0.604	-0.618	Not available	-1.902
Metformin-sitagliptin	-0.462	-0.588	-1.127	-1.407
Metformin-sulfonylurea	-0.665	-0.557	+1.354	+0.896
Metformin-vildagliptin	-0.629	Not available	-0.441	-0.601
Pioglitazone-sulfonylurea[b]	-0.507	-0.430	Not available	+5.806

(a) HbA1c reductions based on an individual with baseline Hba1c equal to 7.5%
(b) Treatment options in italics were not included in the base case original health economic model

Table 78: Absolute treatment effects modelled for additional treatment options in year 2 sensitivity analyses

Treatment	Probability of dropout due to intolerance	Annual rate all hypoglycaemic episodes
Metformin-nateglinide	0.033	0.500
Metformin-saxagliptin	0.036	0.026
Pioglitazone-sulfonylurea	0.033	0.715

Table 79: Drug consumables and staff time resource usage assumptions for additional treatment options in year 2 sensitivity analyses

Therapy level	Treatment	SMBG /day	Needles/day	Sharps bin	Nurse initiation
First intensification	Metformin-nateglinide	0	0	No	No
	Metformin-saxagliptin	0	0	No	No
	Pioglitazone-sulfonylurea	0.429	0	No	No

For the 3 new treatment options, absolute treatment effects modelled for treatment dropout due to intolerance and annual all hypoglycaemia rates are shown in table 78.

Drug unit costs for nateglinide and saxagliptin are shown in table 63. Resource use for the newly included treatment options followed the same assumptions given in 3.9 and are shown in table 79. Weighted average daily doses and annual treatment costs are shown in Table 80.

Metformin dose for metformin-saxagliptin was unknown, so the average metformin dose from metformin-vildagliptin RCTs was used (see 3.8.2).

Table 80: Weighted average daily doses from included RCTs and annual treatment costs – for additional treatment options in year 2 sensitivity analyses

Treatment	Daily dose (mg)		Daily drug cost		Annual treatment cost	
	Year 1	Year 2 onwards	Year 1	Year 2 onwards	Year 1	Year 2 onwards
Metformin-nateglinide			£0.81	£0.91	£296.13	£330.62
Metformin	1513.3	1852.5				
Nateglinide	201.1	326.5				
Metformin-saxagliptin			£1.20	£1.20	£437.62	£437.62
Metformin	1926.33	1926.33				
Saxagliptin	5.0	5.0				
Pioglitazone-sulfonylurea			£0.12	£0.13	£95.19	£100.80
Pioglitazone	18.5	37.0				
Sulfonylurea	71.8	143.6				

3.11.2.2 Weight profiles

The GDG chose to adopt conservative weight profiles in the base case (see section 3.2.6): treatment-related weight-loss would be regained after 1 year, whereas treatment-related weight gain would remain forever (see 3.2.6). Two alternative weight profiles were considered as sensitivity analyses.

Firstly, treatment-related weight-loss was assumed to be regained more gradually, over the period the treatment was taken (i.e. up to the next treatment intensification), rather than only lasting 1 year (see figure 7). Treatment-related weight-gain was assumed to be lost gradually, over the remaining lifetime of the modelled person.

Secondly, treatment-related weight-gain was assumed to be lost after 1 year, in line with the clinical evidence (see figure 8).

We also configured the model to be capable of simulating a third scenario, in which treatment-related weight-changes – whether positive or negative – were assumed to be permanent. However, this was such an unrealistic assumption, in the GDG's views, that we have not reported it even as a sensitivity analysis.

3.11.2.3 Assumed daily drug dose

As explained in 3.8.2, base-case drug cost calculations relied on drug dosages derived from weighted average dosages from the included RCTs. The previous guideline (National Institute for Health and Care Excellence 2009) used assumed daily drug doses, rather than RCT-based weighted averages. Whilst it is a strength of the original health economic model that treatment costs and magnitude of treatment effect were related, we acknowledge that some of the treatment options may not accurately reflect doses used in clinical practice. This was particularly an issue at second intensification, where many treatment options were represented by single RCTs. For this reason, sensitivity analyses were undertaken using assumed daily drug doses rather than weighted RCT average drug doses. It should be noted

that there is no guarantee that the doses used in this analysis would produce the effect size modelled.

Where available, we took assumed daily doses from WHO defined daily doses (World Health Organisation 2014). WHO defined daily doses were not available for insulins. Therefore, we based assumed insulin daily doses the previous guideline (National Institute for Health and Care Excellence 2009) which used 0.55 units/kg/day for long-acting insulins. The baseline weight of people at second intensification here was 86.7 kg (see table 20); thus an assumed daily dose of 47.7 units was used. In the absence of other detail, this dose was also used for biphasic insulins. No adjustments to insulin doses were made to reflect concomitant oral medications. Other published CUAs have used lower insulin doses per kilogram bodyweight, ranging from 0.28 units/kg/day (Woehl et al. 2008) to 0.4 units/kg/day (McEwan et al. 2007).

The previous guideline (National Institute for Health and Care Excellence 2009) assumed an 18% higher dose for insulin detemir than for other long-acting insulins and the same assumption was applied here (giving an assumed daily dose of insulin detemir of 56.2 units). It is interesting to note that the included studies in this guideline displayed around an 18% higher dose for insulin detemir over insulin glargine, which provides good substantiation for this figure.

Table 81: Assumed daily drug doses for sensitivity analysis

Therapy Type	Drug	Assumed daily dose
Oral Drugs	Linagliptin	5 mg
	Metformin	2000 mg
	Pioglitazone	30 mg
	Repaglinide	4.5 mg
	Sitagliptin	100 mg
	Sulfonylurea (gliclazide)	160 mg
	Vildagliptin	100 mg
GLP-1 agonists	Exenatide	2 doses
	Liraglutide	1.2 mg
Insulins	Biphasic human insulin	47.7 units
	Biphasic insulin aspart	47.7 units
	Insulin degludec	47.7 units
	Insulin detemir	56.2 units
	Insulin glargine	47.7 units
	Insulin lispro mix 50/50	47.7 units
	Insulin lispro mix 75/25	47.7 units
	NPH insulin	47.7 units

3.11.2.4 Baseline hypoglycaemia rates

Baseline rates of hypoglycaemia were sourced from existing literature (see section 3.5.4) and relativities for each treatment option were applied from the clinical review. Whilst this means that alternative baseline rates will not alter the incremental results between treatments, they may alter the overall impact of hypoglycaemia on the results. Therefore, we undertook sensitivity analyses with hypoglycaemia rates half and double those used in the base-case analysis.

3.11.2.5 Treatment effect adjustment for baseline HbA1c

The base-case evidence synthesis model included a variable that adjusted the treatment effect based on the baseline HbA1c (see 3.5.1). Sensitivity analyses were undertaken where the treatment effect was not adjusted for baseline HbA1c.

3.12 Summary of original health economic model parameters, sources and distributions

Table 82: Original health economic model parameters

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Discount rate			
Costs	3.5%	NICE (2013)	
Effects	3.5%	NICE (2013)	
Hypoglycaemia rates			
Second intensification			
Baseline rate of hypoglycaemic episodes per year (NPH insulin mix 70/30-Metformin)	14.600 (12.414, 17.171)	Donnelly et al. (2005)	Lognormal: μ=2.681; σ=0.083
Proportion of hypoglycaemic episodes that are severe	0.021 (0.007, 0.043)	Donnelly et al. (2005)	Beta: α=5.000; β=231.000
Initial therapy			
Rate of severe hypoglycaemic episodes treated by NHS on sulfonylurea	0.0089 (0.0060, 0.0131)	Leese et al. (2003)	Lognormal: μ=-4.7267; σ=0.2000
Annual rate of all hypoglycaemic episodes on sulfonylurea	0.794	Calculated field	
First intensification			
Adjusted odds ratio of hypoglycaemia on metformin-sulfonylurea	4.040 (3.274, 4.986)	Bodmer et al. (2008)	Lognormal: μ=1.396; σ=0.107
Adjusted odds ratio of hypoglycaemia on sulfonylurea	2.790 (2.227, 3.495)	Bodmer et al. (2008)	Lognormal: μ=1.026; σ=0.115
Annual rate of all hypoglycaemic episodes on metformin-sulfonylurea	1.014	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Complication costs			
Non-fatal event – year of event			
Inpatient (2000)			
No complications	£157.00 (£144.75, £169.74)	Clarke et al. (2003)	Gamma: α=£606.00; β=£0.26
IHD (macro)	£1,959.00 (£1,463.03, £2,526.24)	Clarke et al. (2003)	Gamma: α=£51.99; β=£37.68
MI (macro)	£4,070.00 (£3,519.00, £4,660.49)	Clarke et al. (2003)	Gamma: α=£195.17; β=£20.85
Heart failure (macro)	£2,221.00 (£1,659.32, £2,863.30)	Clarke et al. (2003)	Gamma: α=£52.11; β=£42.62
Stroke (macro)	£2,367.00 (£1,604.77, £3,275.01)	Clarke et al. (2003)	Gamma: α=£30.68; β=£77.14
Amputation (micro)	£8,459.00 (£4,979.43, £12,845.48)	Clarke et al. (2003)	Gamma: α=£17.60; β=£480.76
Blindness (micro)	£872.00 (£529.30, £1,298.86)	Clarke et al. (2003)	Gamma: α=£19.55; β=£44.60
Outpatient (2000)			
No complications	£159.00 (£147.22, £171.22)	Clarke et al. (2003)	Gamma: α=£674.42; β=£0.24
Macrovascular	£315.00 (£245.82, £392.63)	Clarke et al. (2003)	Gamma: α=£70.56; β=£4.46
Microvascular	£273.00 (£212.78, £340.62)	Clarke et al. (2003)	Gamma: α=£69.90; β=£3.91
Total costs – year of event (2000)			
No complications	£316.00	Calculated field	
IHD	£2,274.00	Calculated field	
MI	£4,385.00	Calculated field	
Heart failure	£2,536.00	Calculated field	
Stroke	£2,682.00	Calculated field	
Amputation	£8,732.00	Calculated field	
Blindness	£1,145.00	Calculated field	
PSSRU HCHS multiplier			
2000	196.5	Curtis (2007)	
2012	289.1	Curtis (2014)	
Total costs – year of event (2012)			
No complications	£464.91	Calculated field	
IHD	£3,345.62	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
MI	£6,451.42	Calculated field	
Heart failure	£3,731.08	Calculated field	
Stroke	£3,945.88	Calculated field	
Amputation	£12,846.93	Calculated field	
Blindness	£1,684.58	Calculated field	
Fatal event – year of event (2000)			
IHD (not used in UKPDS)	£0.00		
MI	£1,152.00 (£935.77, £1,390.37)	Clarke et al. (2003)	Gamma: α=£98.50; β=£11.70
Heart failure (same as non-fatal)	£2,536.00	Calculated field	
Stroke	£3,383.00 (£1,867.06, £5,342.05)	Clarke et al. (2003)	Gamma: α=£14.39; β=£235.12
Amputation (same as non-fatal)	£8,732.00	Calculated field	
Blindness (not used in UKPDS)	£0.00		
Total costs – year of event (2012)			
IHD (not used in UKPDS)	£0.00		
MI	£1,694.88	Calculated field	
Heart failure (same as non-fatal)	£3,731.08	Calculated field	
Stroke	£4,977.23	Calculated field	
Amputation (same as non-fatal)	£12,846.93	Calculated field	
Blindness (not used in UKPDS)	£0.00		
Non-fatal event – subsequent years			
Inpatient (2000)			
No complications (same as non-fatal)	£157.00	Calculated field	
IHD (macro)	£493.00 (£391.84, £605.61)	Clarke et al. (2003)	Gamma: α=£81.55; β=£6.05
MI (macro)	£464.00 (£368.97, £569.75)	Clarke et al. (2003)	Gamma: α=£81.88; β=£5.67
Heart failure (macro)	£631.00 (£409.03, £900.32)	Clarke et al. (2003)	Gamma: α=£25.17; β=£25.07
Stroke (macro)	£249.00 (£162.82, £353.19)	Clarke et al. (2003)	Gamma: α=£26.11; β=£9.53
Amputation (micro)	£300.00 (£142.14, £515.82)	Clarke et al. (2003)	Gamma: α=£9.73; β=£30.83
Blindness (micro)	£281.00 (£185.17, £396.49)	Clarke et al. (2003)	Gamma: α=£27.00; β=£10.41

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Outpatient (2000)			
No complications (same as non-fatal)	£159.00	Calculated field	
Macrovascular	£258.00 (£224.65, £293.62)	Clarke et al. (2003)	Gamma: α=£214.83; β=£1.20
Microvascular	£204.00 (£168.68, £242.63)	Clarke et al. (2003)	Gamma: α=£116.78; β=£1.75
Total costs – year of event (2000)			
No complications	£316.00	Calculated field	
IHD	£751.00	Calculated field	
MI	£722.00	Calculated field	
Heart failure	£889.00	Calculated field	
Stroke	£507.00	Calculated field	
Amputation	£504.00	Calculated field	
Blindness	£485.00	Calculated field	
Total costs – year of event (2012)			
No complications	£464.91	Calculated field	
IHD	£1,104.91	Calculated field	
MI	£1,062.24	Calculated field	
Heart failure	£1,307.94	Calculated field	
Stroke	£745.92	Calculated field	
Amputation	£741.51	Calculated field	
Blindness	£713.55	Calculated field	
Renal failure (macro) costs			
Inpatient costs – year of event (1996)			
Non-fatal	£20,802.00 (£19,618.47, £22,019.70)	Lamping et al. (2000)	Gamma: α=£1,153.01; β=£18.04
Fatal (same as non-fatal)	£20,802.00	Calculated field	
Inpatient costs – subsequent years (1996)			
Non-fatal (same as year of event)	£20,802.00	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Outpatient costs – year of event (2000)			
Non-fatal	£315.00	Calculated field	
Fatal	£315.00	Calculated field	
Outpatient costs – subsequent years (2000)			
Non-fatal	£258.00	Calculated field	
PSSRU HCHS multiplier			
1996	170.6	Curtis (2007)	
2000	196.5	Curtis (2007)	
2012	289.1	Curtis (2014)	
Total costs – year of event (2012)			
Non-fatal	£35,714.66	Calculated field	
Fatal	£35,714.66	Calculated field	
Total costs - subsequent years (2012)			
Non-fatal	£35,360.80	Calculated field	
Adverse event costs			
Severe hypoglycaemic episode managed in community (NHS cost per event)	£231.00 (£149.49, £329.96)	Hammer et al. (2009)	Gamma: α=£25.00; β=£9.24[(a)]
Severe hypoglycaemic episode managed in hospital (NHS cost per event)	£862.00 (£557.84, £1,231.28)	Hammer et al. (2009)	Gamma: α=£25.00; β=£34.48[(a)]
% of hypoglycaemic episodes treated by NHS	0.53 (0.31, 0.74)	Hammer et al. (2009)	Beta: α=10.00; β=9.00
% of severe hypoglycaemic episodes managed in community	0.35 (0.22, 0.49)	Hammer et al. (2009)	Beta: α=15.90; β=29.53[(a)]
Average cost severe hypoglycaemic episode (2007)	£337.45	Calculated field	
PSSRU HCHS multiplier			
2007	257.0	Curtis (2014)	
2012	289.1	Curtis (2014)	
Average cost of severe hypoglycaemic episode (2012)	£379.60		
Treatment switches due to AEs: GP appt (11.7 mins)	£45.00 (£29.12, £64.28)	Curtis (2014)	Gamma: α=£25.00; β=£1.80[(a)]

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Drug unit costs			
Tablets			
Linagliptin			
Tablet size (mg)	5.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	28	NHS Drug Tariff (2014)	
Pack cost	£33.26	NHS Drug Tariff (2014)	
Cost per mg	£0.23757	Calculated field	
Metformin			
Tablet size (mg)	850.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	56	NHS Drug Tariff (2014)	
Pack cost	£1.72	NHS Drug Tariff (2014)	
Cost per mg	£0.00004	Calculated field	
Nateglinide			
Tablet size (mg)	120.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	84	NHS Drug Tariff (2014)	
Pack cost	£25.88	NHS Drug Tariff (2014)	
Cost per mg	£0.00257	Calculated field	
Pioglitazone			
Tablet size (mg)	45.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	28	NHS Drug Tariff (2014)	
Pack cost	£1.65	NHS Drug Tariff (2014)	
Cost per mg	£0.00131	Calculated field	
Repaglinide			
Tablet size (mg)	2.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	90	NHS Drug Tariff (2014)	
Pack cost	£5.79	NHS Drug Tariff (2014)	
Cost per mg	£0.03217	Calculated field	
Saxagliptin			

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Tablet size (mg)	5.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	28	NHS Drug Tariff (2014)	
Pack cost	£31.60	NHS Drug Tariff (2014)	
Cost per mg	£0.22571	Calculated field	
Sitagliptin			
Tablet size (mg)	100.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	28	NHS Drug Tariff (2014)	
Pack cost	£33.26	NHS Drug Tariff (2014)	
Cost per mg	£0.01188	Calculated field	
Sulfonylurea (assume gliclazide)			
Tablet size (mg)	80	NHS Drug Tariff (2014)	
Pack size (number of tablets)	28	NHS Drug Tariff (2014)	
Pack cost	£1.32	NHS Drug Tariff (2014)	
Cost per mg	£0.00059	Calculated field	
Vildagliptin			
Tablet size (mg)	50.0	NHS Drug Tariff (2014)	
Pack size (number of tablets)	56	NHS Drug Tariff (2014)	
Pack cost	£31.76	NHS Drug Tariff (2014)	
Cost per mg	£0.01134	Calculated field	
GLP-1 agonists			
Exenatide (Byetta)			
Pack size (doses)	60.0	NHS Drug Tariff (2014)	
Pack cost	£68.24	NHS Drug Tariff (2014)	
Cost per dose	£1.1373	Calculated field	
Liraglutide (Victoza)			
Pack size (mg)	36.0	NHS DMD (2014)	
Pack cost	£78.48	NHS DMD (2014)	
Cost per mg	£2.1800	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Insulins			
NPH insulin (weighted average Insulatard, Humulin I, Insuman)			
Average cost per unit	£0.01381	HSCIC (2014), NHS DMD (2014)	
Insulin glargine (Lantus)			
Average cost per unit	£0.02778	HSCIC (2014), NHS DMD (2014)	
Insulin detemir (Levemir)			
Average cost per unit	£0.02804	HSCIC (2014), NHS DMD (2014)	
Insulin degludec (Tresiba)			
Average cost per unit	£0.04800	HSCIC (2014), NHS DMD (2014)	
Biphasic insulin aspart (NovoMix 30)			
Average cost per unit	£0.01970	HSCIC (2014), NHS DMD (2014)	
Biphasic insulin lispro (Humalog Mix25)			
Average cost per unit	£0.02004	HSCIC (2014), NHS DMD (2014)	
Biphasic insulin lispro (Humalog Mix50)			
Average cost per unit	£0.02030	HSCIC (2014), NHS DMD (2014)	
Drug treatment cost per day - year 1			
Initial therapy (year 1)			
Metformin	£0.06 (£0.04, £0.09)	Calculated field	Gamma: α=£25.00; β=£0.002[(a)]
Pioglitazone	£0.05 (£0.03, £0.07)	Calculated field	Gamma: α=£25.00; β=£0.002[(a)]
Placebo	£0.00	GDG assumption	
Repaglinide	£0.12 (£0.08, £0.18)	Calculated field	Gamma: α=£25.00; β=£0.005[(a)]

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Sitagliptin	£1.00 (£0.65, £1.43)	Calculated field	Gamma: α=£25.00; β=£0.040[(a)]
Sulfonylurea	£0.09 (£0.06, £0.13)	Calculated field	Gamma: α=£25.00; β=£0.004[(a)]
Vildagliptin	£1.06 (£0.69, £1.52)	Calculated field	Gamma: α=£25.00; β=£0.042[(a)]
First intensification (year 1)			
Exenatide-metformin	£2.35 (£1.52, £3.35)	Calculated field	Gamma: α=£25.00; β=£0.094[(a)]
Linagliptin-metformin	£1.24 (£0.80, £1.77)	Calculated field	Gamma: α=£25.00; β=£0.050[(a)]
Liraglutide-metformin	£2.92 (£1.89, £4.17)	Calculated field	Gamma: α=£25.00; β=£0.117[(a)]
Metformin-nateglinide	£0.81 (£0.52, £1.16)	Calculated field	Gamma: α=£25.00; β=£0.032[(a)]
Metformin-pioglitazone	£0.11 (£0.07, £0.15)	Calculated field	Gamma: α=£25.00; β=£0.004[(a)]
Metformin-saxagliptin	£1.20 (£0.78, £1.71)	Calculated field	Gamma: α=£25.00; β=£0.048[(a)]
Metformin-sitagliptin	£1.26 (£0.81, £1.80)	Calculated field	Gamma: α=£25.00; β=£0.050[(a)]
Metformin-sulfonylurea	£0.14 (£0.09, £0.20)	Calculated field	Gamma: α=£25.00; β=£0.006[(a)]
Metformin-vildagliptin	£1.20 (£0.78, £1.72)	Calculated field	Gamma: α=£25.00; β=£0.048[(a)]
Pioglitazone-sulfonylurea	£0.12 (£0.08, £0.17)	Calculated field	Gamma: α=£25.00; β=£0.005[(a)]
Second intensification (year 1)			
Biphasic insulin aspart-metformin	£0.91 (£0.59, £1.29)	Calculated field	Gamma: α=£25.00; β=£0.036[(a)]
Biphasic insulin aspart-metformin-sulfonylurea	£0.67 (£0.44, £0.96)	Calculated field	Gamma: α=£25.00; β=£0.027[(a)]
Biphasic insulin aspart-repaglinide	£0.50 (£0.33, £0.72)	Calculated field	Gamma: α=£25.00; β=£0.020[(a)]
Exenatide-metformin-sulfonylurea	£2.35 (£1.52, £3.36)	Calculated field	Gamma: α=£25.00; β=£0.094[(a)]
Insulin degludec/aspart mix-metformin	£0.64 (£0.41, £0.91)	Calculated field	Gamma: α=£25.00; β=£0.025[(a)]
Insulin degludec-metformin	£1.88 (£1.21, £2.68)	Calculated field	Gamma: α=£25.00; β=£0.075[(a)]
Insulin detemir-metformin	£1.35 (£0.88, £1.93)	Calculated field	Gamma: α=£25.00; β=£0.054[(a)]
Insulin glargine-metformin	£1.25 (£0.81, £1.78)	Calculated field	Gamma: α=£25.00; β=£0.050[(a)]
Insulin glargine-metformin-sulfonylurea	£0.76 (£0.49, £1.09)	Calculated field	Gamma: α=£25.00; β=£0.030[(a)]
Insulin glargine-sulfonylurea	£0.94 (£0.61, £1.35)	Calculated field	Gamma: α=£25.00; β=£0.038[(a)]
Insulin lispro mix 50 and mix 25	£0.78 (£0.51, £1.12)	Calculated field	Gamma: α=£25.00; β=£0.031[(a)]
Insulin lispro mix 50/50-metformin	£1.36 (£0.88, £1.94)	Calculated field	Gamma: α=£25.00; β=£0.054[(a)]
Liraglutide-metformin-sulfonylurea	£3.98 (£2.57, £5.68)	Calculated field	Gamma: α=£25.00; β=£0.159[(a)]

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Metformin-NPH insulin	£0.74 (£0.48, £1.05)	Calculated field	Gamma: α=£25.00; β=£0.029[(a)]
Metformin-NPH insulin-repaglinide	£0.64 (£0.42, £0.92)	Calculated field	Gamma: α=£25.00; β=£0.026[(a)]
Metformin-NPH insulin-sulfonylurea	£0.52 (£0.34, £0.74)	Calculated field	Gamma: α=£25.00; β=£0.021[(a)]
Metformin-Pioglitazone-sulfonylurea	£0.23 (£0.15, £0.33)	Calculated field	Gamma: α=£25.00; β=£0.009[(a)]
Metformin-sitagliptin-sulfonylurea	£1.40 (£0.91, £2.00)	Calculated field	Gamma: α=£25.00; β=£0.056[(a)]
NPH insulin	£0.66 (£0.43, £0.94)	Calculated field	Gamma: α=£25.00; β=£0.026[(a)]
NPH insulin-sulfonylurea	£0.52 (£0.33, £0.74)	Calculated field	Gamma: α=£25.00; β=£0.021[(a)]
Initial therapy (year 2 onwards)			
Metformin	£0.07 (£0.04, £0.09)	Calculated field	Gamma: α=£25.00; β=£0.003[(a)]
Pioglitazone	£0.06 (£0.04, £0.08)	Calculated field	Gamma: α=£25.00; β=£0.002[(a)]
Placebo	£0.00	GDG assumption	
Repaglinide	£0.13 (£0.08, £0.18)	Calculated field	Gamma: α=£25.00; β=£0.005[(a)]
Sitagliptin	£1.00 (£0.65, £1.43)	Calculated field	Gamma: α=£25.00; β=£0.040[(a)]
Sulfonylurea	£0.09 (£0.06, £0.13)	Calculated field	Gamma: α=£25.00; β=£0.004[(a)]
Vildagliptin	£1.06 (£0.69, £1.52)	Calculated field	Gamma: α=£25.00; β=£0.042[(a)]
First intensification (year 2 onwards)			
Exenatide-metformin	£2.35 (£1.52, £3.35)	Calculated field	Gamma: α=£25.00; β=£0.094[(a)]
Linagliptin-metformin	£1.24 (£0.80, £1.77)	Calculated field	Gamma: α=£25.00; β=£0.050[(a)]
Liraglutide-metformin	£2.94 (£1.90, £4.19)	Calculated field	Gamma: α=£25.00; β=£0.117[(a)]
Metformin-nateglinide	£0.91 (£0.59, £1.29)	Calculated field	Gamma: α=£25.00; β=£0.036[(a)]
Metformin-pioglitazone	£0.11 (£0.07, £0.16)	Calculated field	Gamma: α=£25.00; β=£0.004[(a)]
Metformin-saxagliptin	£1.20 (£0.78, £1.71)	Calculated field	Gamma: α=£25.00; β=£0.048[(a)]
Metformin-sitagliptin	£1.26 (£0.81, £1.80)	Calculated field	Gamma: α=£25.00; β=£0.050[(a)]
Metformin-sulfonylurea	£0.15 (£0.10, £0.22)	Calculated field	Gamma: α=£25.00; β=£0.006[(a)]
Metformin-vildagliptin	£1.20 (£0.78, £1.72)	Calculated field	Gamma: α=£25.00; β=£0.048[(a)]
Pioglitazone-sulfonylurea	£0.13 (£0.09, £0.19)	Calculated field	Gamma: α=£25.00; β=£0.005[(a)]
Second intensification (year 2 onwards)			
Biphasic insulin aspart-metformin	£1.08 (£0.70, £1.54)	Calculated field	Gamma: α=£25.00; β=£0.043[(a)]

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Biphasic insulin aspart-metformin-sulfonylurea	£0.78 (£0.51, £1.12)	Calculated field	Gamma: α=£25.00; β=£0.031[(a)]
Biphasic insulin aspart-repaglinide	£0.72 (£0.47, £1.03)	Calculated field	Gamma: α=£25.00; β=£0.029[(a)]
Exenatide-metformin-sulfonylurea	£2.44 (£1.58, £3.49)	Calculated field	Gamma: α=£25.00; β=£0.098[(a)]
Insulin degludec/aspart mix-metformin	£0.70 (£0.45, £1.00)	Calculated field	Gamma: α=£25.00; β=£0.028[(a)]
Insulin degludec-metformin	£2.09 (£1.35, £2.98)	Calculated field	Gamma: α=£25.00; β=£0.084[(a)]
Insulin detemir-metformin	£1.69 (£1.09, £2.41)	Calculated field	Gamma: α=£25.00; β=£0.068[(a)]
Insulin glargine-metformin	£1.42 (£0.92, £2.03)	Calculated field	Gamma: α=£25.00; β=£0.057[(a)]
Insulin glargine-metformin-sulfonylurea	£0.87 (£0.56, £1.24)	Calculated field	Gamma: α=£25.00; β=£0.035[(a)]
Insulin glargine-sulfonylurea	£1.06 (£0.68, £1.51)	Calculated field	Gamma: α=£25.00; β=£0.042[(a)]
Insulin lispro mix 50 and mix 25	£0.90 (£0.58, £1.28)	Calculated field	Gamma: α=£25.00; β=£0.036[(a)]
Insulin lispro mix 50/50-metformin	£1.40 (£0.90, £2.00)	Calculated field	Gamma: α=£25.00; β=£0.056[(a)]
Liraglutide-metformin-sulfonylurea	£4.08 (£2.64, £5.82)	Calculated field	Gamma: α=£25.00; β=£0.163[(a)]
Metformin-NPH insulin	£0.87 (£0.56, £1.25)	Calculated field	Gamma: α=£25.00; β=£0.035[(a)]
Metformin-NPH insulin-repaglinide	£0.70 (£0.45, £1.00)	Calculated field	Gamma: α=£25.00; β=£0.028[(a)]
Metformin-NPH insulin-sulfonylurea	£0.56 (£0.36, £0.80)	Calculated field	Gamma: α=£25.00; β=£0.022[(a)]
Metformin-Pioglitazone-sulfonylurea	£0.23 (£0.15, £0.34)	Calculated field	Gamma: α=£25.00; β=£0.009[(a)]
Metformin-sitagliptin-sulfonylurea	£1.40 (£0.91, £2.00)	Calculated field	Gamma: α=£25.00; β=£0.056[(a)]
NPH insulin	£0.87 (£0.56, £1.24)	Calculated field	Gamma: α=£25.00; β=£0.035[(a)]
NPH insulin-sulfonylurea	£0.57 (£0.37, £0.82)	Calculated field	Gamma: α=£25.00; β=£0.023[(a)]
Unit costs - consumables and staff time			
Needles - weighted average cost per needle	£0.11	HSCIC (2014)	
Sharps bins - average cost per bin	£0.85	HSCIC (2014)	
Bins per year	3.0	GDG assumption	
Cost per day	£0.01	Calculated field	
Self monitoring of blood glucose			
Test strips - weighted average cost per strip	£0.29	HSCIC (2014)	
Lancets - weighted average cost per lancet	£0.04	HSCIC (2014)	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Cost per SMBG test	£0.33	Calculated field	
Insulin initiation costs			
Total time required	3.0	HSCIC (2014)	Triangular: min=0.4; mode=3.0; max=3.0[(b)]
Cost of practice nurse (AFC band 7) per hour	£52.00	Curtis (2014)	
Cost of staff time for insulin initiation	£156.00	Calculated field	
GLP1 Initiation costs			
Total time required	0.67	GDG assumption	Triangular: min=0.08; mode=0.67; max=0.67[(b)]
Cost of practice nurse (AFC band 7) per hour	£52.00	Curtis (2014)	
Cost of staff time for GLP1 initiation	£34.67	Calculated field	
Total treatment cost per year - year 1			
Initial therapy			
Metformin	£22.56	Calculated field	
Pioglitazone	£70.83	Calculated field	
Placebo	£0.00	GDG assumption	
Repaglinide	£44.90	Calculated field	
Sitagliptin	£365.55	Calculated field	
Sulfonylurea	£84.23	Calculated field	
Vildagliptin	£387.97	Calculated field	
First intensification			
Exenatide-metformin	£1,030.15	Calculated field	
Linagliptin-metformin	£453.65	Calculated field	
Liraglutide-metformin	£1,196.24	Calculated field	
Metformin-nateglinide	£296.13	Calculated field	
Metformin-pioglitazone	£91.42	Calculated field	
Metformin-saxagliptin	£437.62	Calculated field	
Metformin-sitagliptin	£459.28	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Metformin-sulfonylurea	£104.32	Calculated field	
Metformin-vildagliptin	£439.71	Calculated field	
Pioglitazone-sulfonylurea	£95.19	Calculated field	
Second intensification			
Biphasic insulin aspart-metformin	£816.77	Calculated field	
Biphasic insulin aspart-metformin-sulfonylurea	£732.16	Calculated field	
Biphasic insulin aspart-repaglinide	£628.21	Calculated field	
Exenatide-metformin-sulfonylurea	£1,032.63	Calculated field	
Insulin degludec/aspart mix-metformin	£676.51	Calculated field	
Insulin degludec-metformin	£1,129.39	Calculated field	
Insulin detemir-metformin	£938.50	Calculated field	
Insulin glargine-metformin	£899.51	Calculated field	
Insulin glargine-metformin-sulfonylurea	£722.13	Calculated field	
Insulin glargine-sulfonylurea	£788.75	Calculated field	
Insulin lispro mix 50 and mix 25	£771.43	Calculated field	
Insulin lispro mix 50/50-metformin	£1,024.52	Calculated field	
Liraglutide-metformin-sulfonylurea	£1,583.30	Calculated field	
Metformin-NPH insulin	£712.74	Calculated field	
Metformin-NPH insulin-repaglinide	£679.25	Calculated field	
Metformin-NPH insulin-sulfonylurea	£634.03	Calculated field	
Metformin-Pioglitazone-sulfonylurea	£135.74	Calculated field	
Metformin-sitagliptin-sulfonylurea	£564.67	Calculated field	
NPH insulin	£725.78	Calculated field	
NPH insulin-sulfonylurea	£632.06	Calculated field	
Total treatment cost per year - year 2 onwards			
Initial therapy			
Metformin	£24.03	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Pioglitazone	£72.93	Calculated field	
Placebo	£0.00	GDG assumption	
Repaglinide	£46.48	Calculated field	
Sitagliptin	£365.55	Calculated field	
Sulfonylurea	£86.48	Calculated field	
Vildagliptin	£387.97	Calculated field	
First intensification			
Exenatide-metformin	£995.48	Calculated field	
Linagliptin-metformin	£453.65	Calculated field	
Liraglutide-metformin	£1,168.54	Calculated field	
Metformin-nateglinide	£330.62	Calculated field	
Metformin-pioglitazone	£93.29	Calculated field	
Metformin-saxagliptin	£437.62	Calculated field	
Metformin-sitagliptin	£459.28	Calculated field	
Metformin-sulfonylurea	£107.64	Calculated field	
Metformin-vildagliptin	£439.71	Calculated field	
Pioglitazone-sulfonylurea	£100.80	Calculated field	
Second intensification			
Biphasic insulin aspart-metformin	£724.47	Calculated field	
Biphasic insulin aspart-metformin-sulfonylurea	£615.23	Calculated field	
Biphasic insulin aspart-repaglinide	£552.26	Calculated field	
Exenatide-metformin-sulfonylurea	£1,029.92	Calculated field	
Insulin degludec/aspart mix-metformin	£544.60	Calculated field	
Insulin degludec-metformin	£1,050.82	Calculated field	
Insulin detemir-metformin	£904.42	Calculated field	
Insulin glargine-metformin	£806.84	Calculated field	
Insulin glargine-metformin-sulfonylurea	£604.57	Calculated field	
Insulin glargine-sulfonylurea	£673.30	Calculated field	

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Insulin lispro mix 50 and mix 25	£656.67	Calculated field	
Insulin lispro mix 50/50-metformin	£882.02	Calculated field	
Liraglutide-metformin-sulfonylurea	£1,585.39	Calculated field	
Metformin-NPH insulin	£606.27	Calculated field	
Metformin-NPH insulin-repaglinide	£543.14	Calculated field	
Metformin-NPH insulin-sulfonylurea	£491.47	Calculated field	
Metformin-Pioglitazone-sulfonylurea	£137.90	Calculated field	
Metformin-sitagliptin-sulfonylurea	£564.67	Calculated field	
NPH insulin	£647.00	Calculated field	
NPH insulin-sulfonylurea	£497.28	Calculated field	
Utility values			
Baseline utility			
UKPDS (male, 58.6 years)	0.785 (0.775, 0.795)	Clarke et al. (2002)	Beta: α=4789.878; β=1311.878
Utility decrements (additive, annual, all years)			
IHD	-0.090 (0.059, 0.131)	Clarke et al. (2002)	Lognormal: μ=-2.428; σ=0.202
MI	-0.055 (0.044, 0.069)	Clarke et al. (2002)	Lognormal: μ=-2.907; σ=0.116
Heart failure	-0.108 (0.060, 0.180)	Clarke et al. (2002)	Lognormal: μ=-2.265; σ=0.280
Stroke	-0.164 (0.113, 0.230)	Clarke et al. (2002)	Lognormal: μ=-1.824; σ=0.181
Amputation	-0.280 (0.186, 0.404)	Clarke et al. (2002)	Lognormal: μ=-1.292; σ=0.198
Blindness	-0.074 (0.040, 0.125)	Clarke et al. (2002)	Lognormal: μ=-2.645; σ=0.287[(c)]
Renal Failure	-0.263 (0.228, 0.302)	Kiberd and Jindal (1995)	Lognormal: μ=-1.338; σ=0.071
Weight-Change			
Utility loss per unit of BMI >25 (annual)	-0.006 (0.004, 0.008)	Bagust and Beale (2005)	Lognormal: μ=-5.113; σ=0.163
Baseline BMI (from UKPDS)	27.700 (27.528, 27.872)	Stratton et al. (2000)	Normal: μ=27.700; σ=0.088
Hypoglycaemia (3 monthly)			
Hypoglycaemia Fear Scale (HFS) change			
Symptomatic hypoglycaemia	1.773 (1.322, 2.224)	Currie et al. (2006)	Normal: μ=1.773; σ=0.230

Parameter	Value (95% confidence interval)	Reference	Distribution and Parameters
Severe hypoglycaemia	5.881 (2.837, 8.925)	Currie et al. (2006)	Normal: μ=5.881; σ=1.553
Multiplier HFS to EQ5D	-0.008 (0.006, 0.010)	Currie et al. (2006)	Lognormal: μ=-4.836; σ=0.125
EQ5D utility decrements			
Symptomatic	-0.014	Calculated field	
Severe	-0.047	Calculated field	
Treatment switches due to AEs (nausea)			
Basic health state	0.890 (0.867, 0.911)	Matza et al. (2007)	Beta: α=664.193; β=82.091
Basic health state with nausea	0.850 (0.821, 0.877)	Matza et al. (2007)	Beta: α=545.258; β=96.222
Duration of utility decrement (in years)	0.115 (0.051, 0.114)	GDG assumption	Triangular: min=0.038; mode=0.115; max=0.115[(b)]
Disutility for medication-related nausea	-0.005	Calculated field	

(a) Standard error unknown, assumed to be 20% of parameter value
(b) Limits of triangular distribution assumed
(c) Published confidence interval from tobit model did not contain point estimate, therefore published confidence interval from CLAD model used to estimate standard error (see 3.11.1)

4 Health economic model – results

For each therapy level, we ran base-case models with 50,000 generated people for 100 UKPDS OM1 'inner' loops; the results presented here are the averages from 1000 'outer' probabilistic iterations. (see 3.2.3). Treatment effects were applied at year 1 and, for initial therapy and first intensification, treatment intensified when HbA1c rose to greater than 7.5%.

4.1 Initial therapy – base-case results

When averaged across all 7 modelled therapies (including placebo) the simulated cohort starting on initial therapy survived for an average of 18.3 undiscounted life years – given an average starting age of 59.8, people survived until an average age of 78.1 years. Irrespective of initial therapy, people intensified to metformin-sulfonylurea then metformin-NPH insulin when each simulated individual's HbA1c rose to a value greater than 7.5%.

As a consequence of the gradual progression of type 2 diabetes and modelled HbA1c progression, after 15 years no-one remained on initial therapy and, after 21 years, all people have intensified to metformin and NPH insulin (see table 83).

Table 83: Initial therapy people on each therapy level by year

Year	Initial therapy	First intensification	Second intensification	Dead
1	99.1%	0.0%	0.0%	0.9%
2	57.8%	39.3%	0.0%	2.9%
3	50.2%	37.6%	7.2%	4.9%
4	40.9%	31.2%	20.8%	7.1%
5	30.4%	26.2%	34.0%	9.4%
6	20.9%	26.9%	40.3%	11.9%
7	13.1%	26.1%	46.3%	14.5%
8	7.2%	23.1%	52.5%	17.3%
9	3.4%	19.1%	57.4%	20.1%
10	1.4%	14.7%	60.9%	23.1%
...				

(a) Years 11 onwards not shown

People were on initial therapy for an average of 3.4 years before intensifying therapy, followed by 3.1 years on first intensification treatment. Time on initial therapy was directly linked to magnitude of HbA1c treatment effect; thus people on placebo and vildagliptin spent least time on initial therapy (see table 84). The intensification of the metformin cohort can be seen in figure 13 (metformin shown as an example as it is the most commonly used existing initial therapy).

Table 84: Years spent on initial therapy

Treatment	Years on initial therapy
Repaglinide->Metformin-Sulfonylurea->Metformin-NPH insulin	3.9
Metformin->Metformin-Sulfonylurea->Metformin-NPH insulin	3.8
Pioglitazone->Metformin-Sulfonylurea->Metformin-NPH insulin	3.8
Sulfonylurea->Metformin-Sulfonylurea->Metformin-NPH insulin	3.6
Sitagliptin->Metformin-Sulfonylurea->Metformin-NPH insulin	3.6
Vildagliptin->Metformin-Sulfonylurea->Metformin-NPH insulin	3.0
Placebo->Metformin-Sulfonylurea->Metformin-NPH insulin	2.3
Average	**3.4**

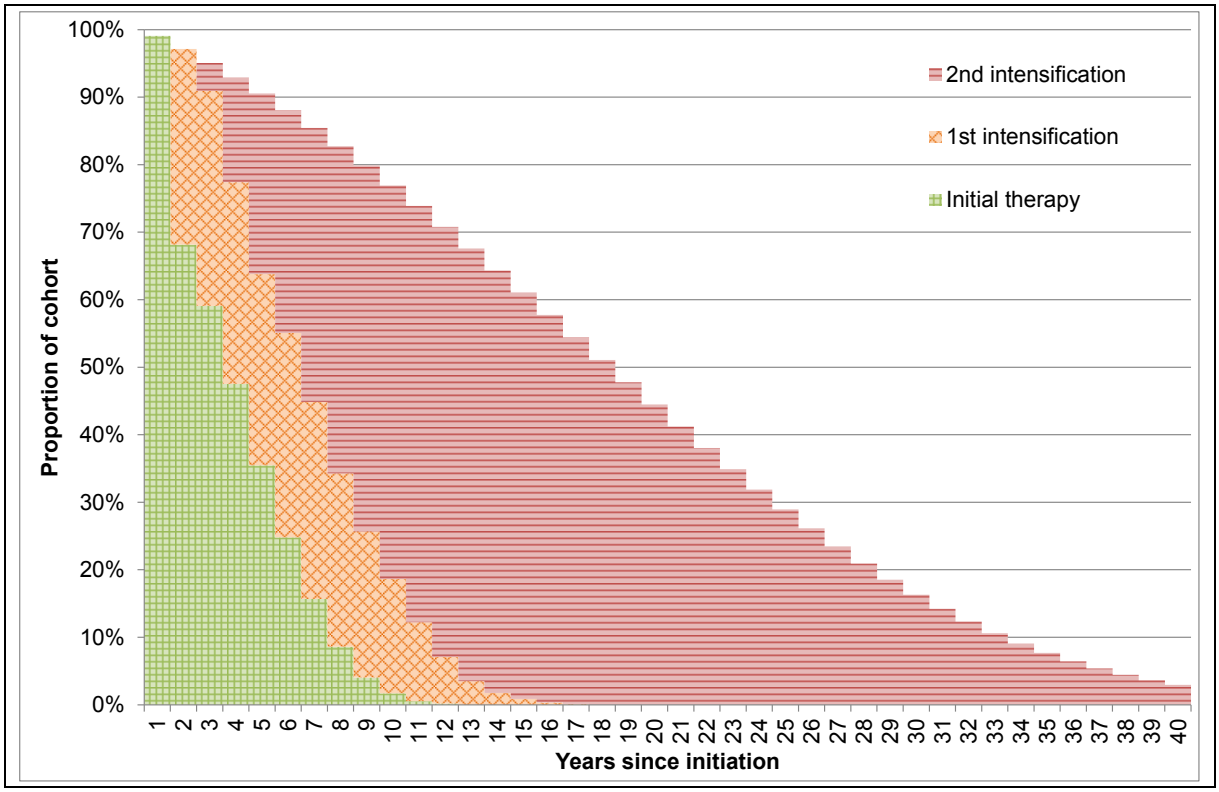


Figure 13: Years spent on each therapy level (metformin)

4.1.1 Clinical outcomes

There was very little difference in complication rates between therapies (see table 85). People on placebo had marginally higher lifetime event-rates than those on active treatments and those on the least effective HbA1c treatment (vildagliptin) had the higher lifetime event-rates of the active treatments.

The lack of differences in complication rates was partly due to small differences in HbA1c treatment effect between treatments, but more due to the normalising effects of treatment intensification. Few people spent long on their initial treatments before intensifying to metformin-sulfonylurea and subsequently to metformin-NPH insulin (see 4.1).

Table 85: Mean lifetime event rates for initial therapy

Initial Therapy	Amputation	Blindness	Renal Failure	CHF	IHD	MI	Stroke	Life Years
Placebo	0.04025	0.08156	0.02601	0.16202	0.13281	0.36191	0.15351	18.259
Vildagliptin	0.03963	0.08068	0.02599	0.16101	0.13215	0.35996	0.15268	18.284
Sulfonylurea	0.03908	0.07984	0.02598	0.16029	0.13163	0.35833	0.15193	18.305
Sitagliptin	0.03916	0.08002	0.02599	0.16025	0.13161	0.35840	0.15200	18.306
Pioglitazone	0.03892	0.07968	0.02597	0.15990	0.13137	0.35773	0.15156	18.315
Metformin	0.03883	0.07957	0.02594	0.15989	0.13134	0.35755	0.15159	18.317
Repaglinide	0.03878	0.07945	0.02592	0.15980	0.13127	0.35736	0.15161	18.320

(a) Results shown are from a single base case model run of 50,000 people through 1000 loops
(b) All treatments intensified to metformin-sulfonylurea then metformin-NPH insulin
(c) Event rates and life years are undiscounted
(d) CHF: congestive heart failure; IHD: ischaemic heart disease; MI: myocardial infarction
(e) For definitions of events, see Appendix F.2 of this document

4.1.2 Lifetime discounted QALYs

People who started the original health economic model at initial therapy gained an average of 9.0 lifetime discounted QALYs (see table 86). As the lifetime event rates for complications were very similar, UKPDS-modelled complications resulted in only marginal differences between QALYs. Most QALYs were lost and most variation in QALY losses were due to weight-change (either treatment-related weight-change or annual weight increases).

Initial therapy with metformin was the treatment that gained most lifetime discounted QALYs. Pioglitazone, sulfonylurea and, to a lesser extent, repaglinide incurred QALYs losses due to their higher weight-gains.

Table 86: Mean lifetime discounted QALYs for initial therapy

Initial Therapy	UKPDS	Hypoglycaemia		Weight	Treatment switches	Total
		Symptomatic	Severe			
Placebo	9.673	-0.284	-0.024	-0.452	-0.001	8.912
Sulfonylurea	9.702	-0.263	-0.022	-0.466	-0.001	8.950
Vildagliptin	9.689	-0.267	-0.023	-0.443	-0.001	8.954
Pioglitazone	9.708	-0.249	-0.021	-0.464	-0.001	8.973
Repaglinide	9.711	-0.256	-0.022	-0.459	-0.001	8.974
Sitagliptin	9.703	-0.254	-0.022	-0.436	-0.001	8.990
Metformin	9.709	-0.248	-0.021	-0.407	-0.001	9.033

(a) All treatments intensified to metformin-sulfonylurea then metformin-NPH insulin
(b) UKPDS: QALYs gained within UKPDS OM1 as a result of survival and long-term complications

4.1.3 Lifetime discounted costs

The biggest proportion of lifetime discounted costs (between 67% and 71%) were incurred as a result of UKPDS OM1 modelled complications (see table 87). However, the costs of the modelled pharmacological treatments themselves accounted for most variation in lifetime discounted costs. Metformin incurred the lowest treatment-related costs, with sitagliptin and vildagliptin incurring the highest treatment-related costs due to their higher unit costs. Accordingly, initial treatment with metformin incurred the lowest lifetime discounted costs. Note that, whilst placebo had no associated treatment cost, quicker intensification to further levels of therapy incurred treatment costs.

Table 87: Mean lifetime discounted costs for initial therapy

Initial Therapy	UKPDS	Treatment Costs	Severe Hypoglycaemia	Treatment switches	Total
Metformin	£13,693	£4852	£697	£8	£19,250
Repaglinide	£13,695	£4890	£707	£6	£19,298
Pioglitazone	£13,700	£5005	£700	£9	£19,413
Sulfonylurea	£13,710	£5133	£728	£9	£19,580
Placebo	£13,758	£5479	£800	£8	£20,044
Sitagliptin	£13,702	£6032	£715	£7	£20,457
Vildagliptin	£13,731	£6137	£752	£7	£20,627

(a) All treatments intensified to metformin-sulfonylurea then metformin-NPH insulin
(b) UKPDS: costs incurred within UKPDS OM1 as a result of survival and long-term complications

4.1.4 Incremental cost–utility results

As initial treatment with metformin incurred the highest lifetime discounted QALYs and the lowest lifetime discounted costs, metformin dominated all other initial therapy treatment options (see table 88 and figure 14).

Table 88: Mean lifetime incremental cost–utility results for initial therapy

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,250	9.033			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,298	8.974	£48	-0.059	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973	£163	-0.060	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£330	-0.082	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£794	-0.121	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1207	-0.043	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£1377	-0.078	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

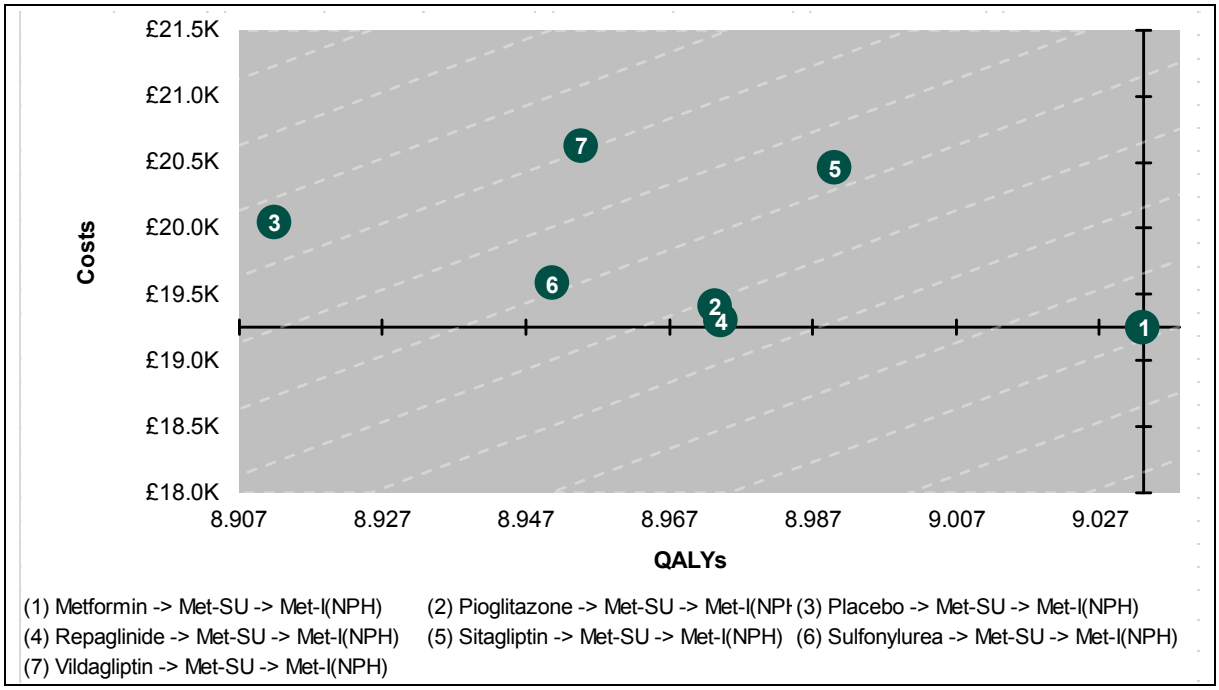


Figure 14: Cost-utility plane for initial therapy

As routine first-line pharmacological therapy with metformin is a mainstay of treatment for type 2 diabetes in the NHS and beyond, it was unsurprising and reassuring that our analysis concluded that this strategy is clearly optimal.

The GDG indicated that the clinical question of greater interest was what initial therapy should be given for people who could not take metformin. When metformin was removed from the decision space, repaglinide became the most cost-effective initial therapy treatment option as the incremental lifetime discounted QALY gain from sitagliptin was outweighed by the incremental cost increase (see table 89).

Readers may note that, when we removed metformin from the initial therapy decision space, the model still assumed that people whose initial therapy provided insufficient HbA1c control would intensify to treatment options containing metformin. This may appear contradictory. However, the GDG felt clinicians would try to continue metformin treatment wherever

possible. Moreover, there was very limited evidence for treatment options not containing metformin at first and second intensification (see 3.4.2 and 3.4.3). This is an acknowledged limitation of the analysis; however, sensitivity analyses provided some reassurance that, had we been able to model a decision space in which metformin was removed entirely, this would have made very little difference to the value for money estimated for initial therapy options (see 4.13).

Table 89: Mean lifetime incremental cost–utility results for initial therapy when metformin was not within the decision space

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,298	8.974			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973	£115	-0.001	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£282	-0.024	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£746	-0.062	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1159	0.016	£73,287
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

In further discussion, the GDG indicated that, for some people who could not take metformin, repaglinide may not be an acceptable treatment option at initial therapy, either. This is due to intolerance or contraindications but, more particularly, due to the lack of a licensed treatment option containing repaglinide but not metformin at first intensification. The GDG were unsure whether patients and clinicians would be willing to start on an initial therapy that then required switching to 2 different drugs at first intensification. Therefore, the decision space was re-analysed with both metformin and repaglinide removed (see table 90). In this instance, pioglitazone was the cheapest treatment option.

Table 90: Mean lifetime incremental cost–utility results for initial therapy when metformin and repaglinide were not within the decision space

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£167	-0.023	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£631	-0.061	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1044	0.017	£62,476
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 91: Mean lifetime incremental cost–utility results for initial therapy when metformin, repaglinide and pioglitazone were not within the decision space

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950			
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£464	-0.039	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£877	0.039	£22,256
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

However, pioglitazone is contra-indicated for a large number of people with type 2 diabetes so again this may not be an acceptable option for people who cannot take metformin. When none of metformin, repaglinide or pioglitazone are treatment options, sulfonylurea was the

cheapest treatment option, but sitagliptin had an ICER of £22,300/QALY compared with sulfonylyurea (see table 91). Compared with sulfonylyrea, the additional treatment costs for sitagliption were offset against fewer lifetime discounted QALYs lost due to weight change.

4.2 Initial therapy – probabilistic sensitivity analyses

Over 1000 PSA iterations, metformin was the most cost-effective initial therapy treatment options in 88% of iterations at a maximum acceptable ICER of £20,000/QALY (see figure 15). Notably, sulfonylurea was consistently the least cost-effective initial therapy treatment option and, at a maximum acceptable ICER of £20,000/QALY, placebo had a higher probability of cost effectiveness.

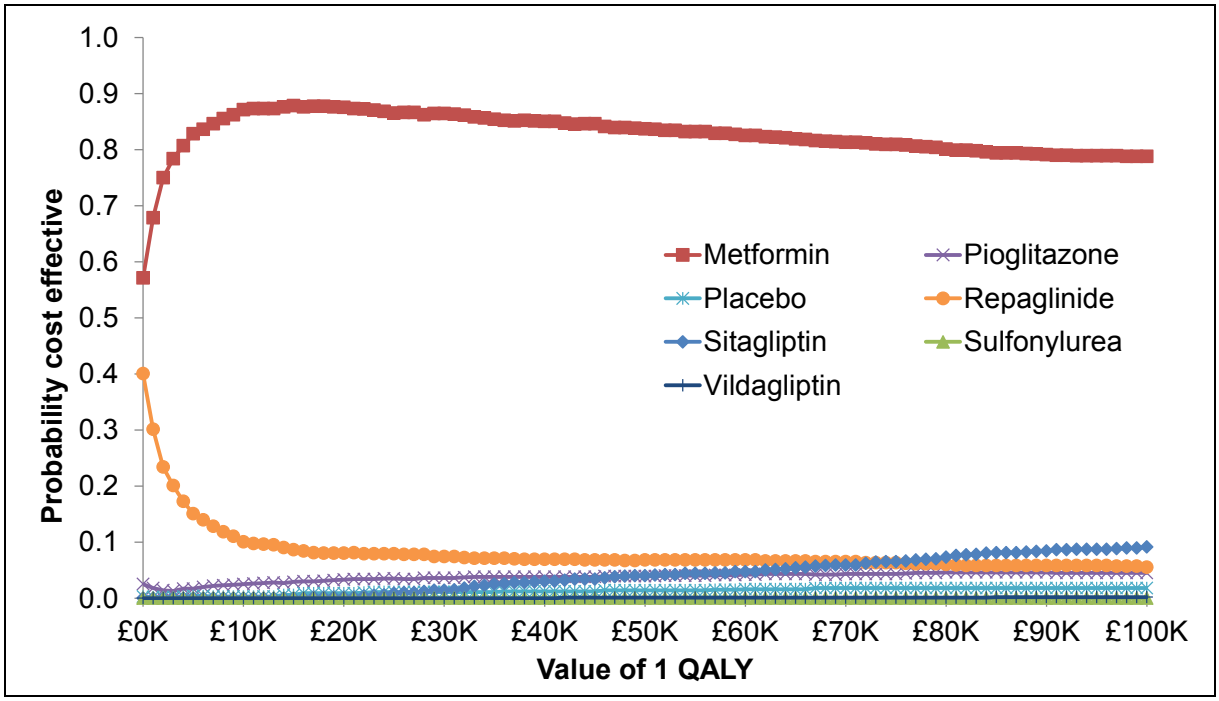


Figure 15: Cost-effectiveness acceptability curve for initial therapy

For people who could not take metformin, repaglinide was the most cost-effective initial therapy treatment option at a maximum acceptable ICER of £20,000/QALY in 45% of iterations, with pioglitazone the most cost-effective initial therapy in 35% of iterations (see figure 16).

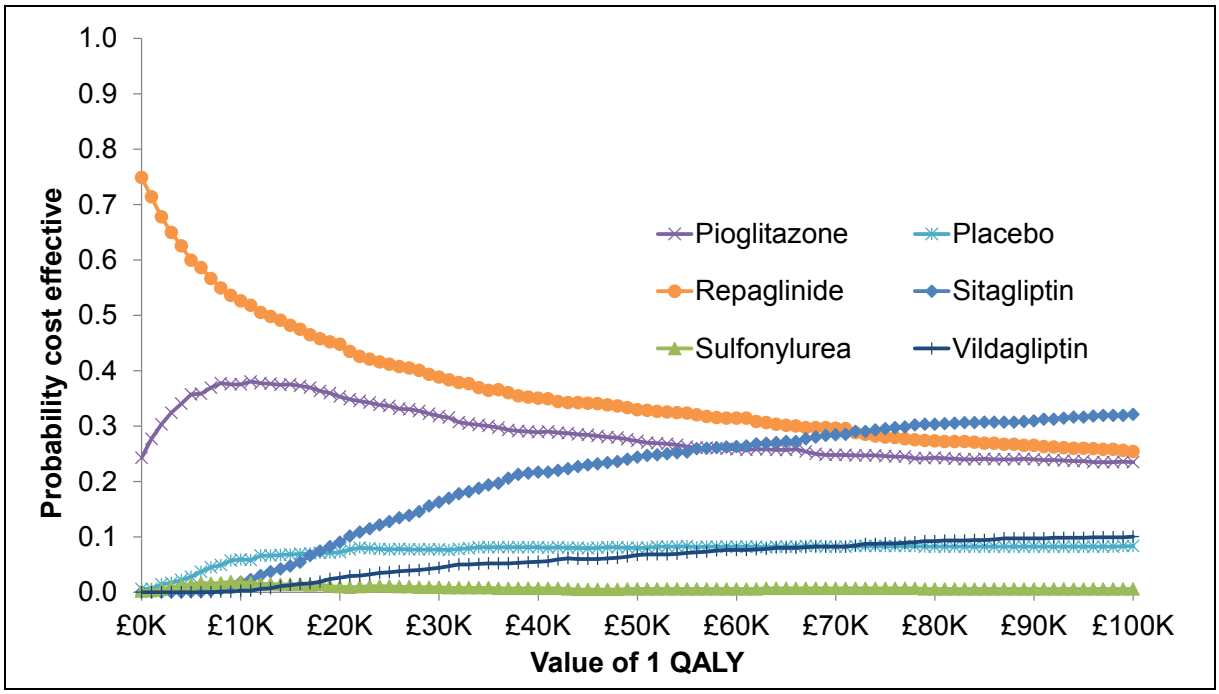


Figure 16: Cost-effectiveness acceptability curve for initial therapy when metformin is not a treatment option

For people who could not tolerate metformin and could not tolerate or choose not to initiate therapy with repaglinide, pioglitazone (most cost-effective in 60% of iterations) and sitagliptin (most cost-effective in 18% of iterations) were the most cost-effective initial therapy treatment options at a maximum acceptable ICER of £20,000/QALY (see figure 17).

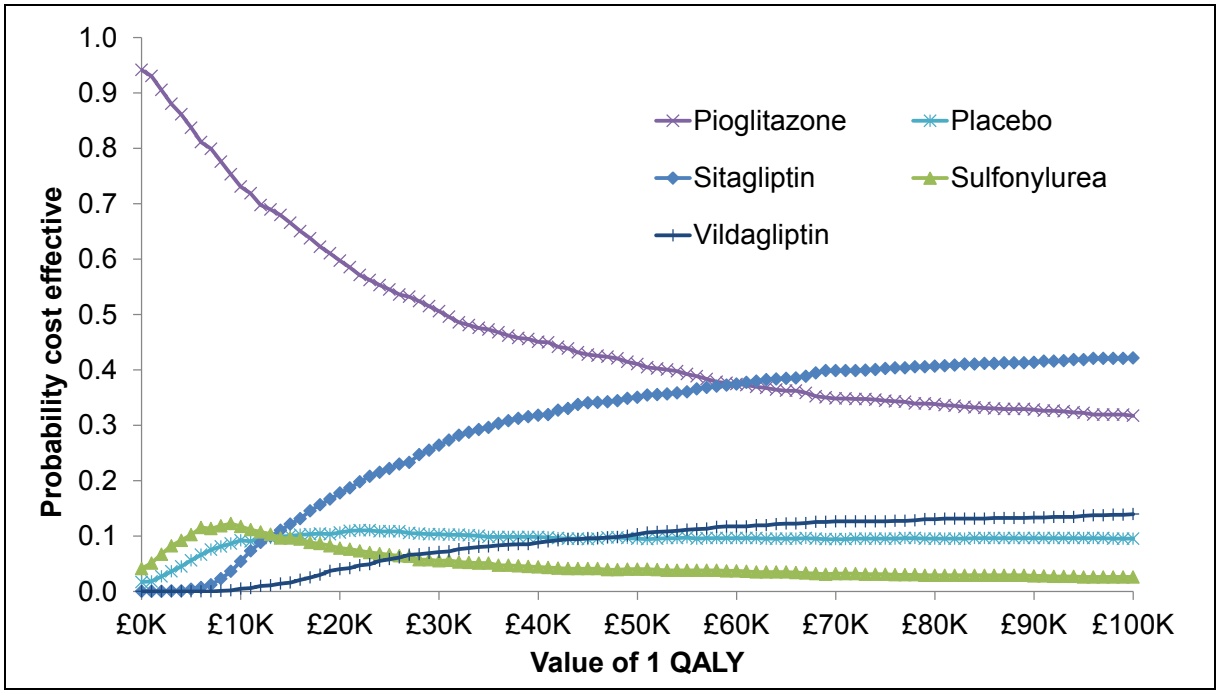


Figure 17: Cost-effectiveness acceptability curve for initial therapy when neither metformin nor repaglinide are treatment options

For people who could not tolerate metformin, could not tolerate or choose not to initiate therapy with repaglinide and were contraindicated for pioglitazone, sitagliptin (most cost-

effective in 38% of iterations) and sulfonylurea (most cost-effective in 37% of iterations) were the most cost-effective initial therapy treatment options at a maximum acceptable ICER of £20,000/QALY (see figure 18). The cost-effective acceptability frontier (CEAF) showed the point at which sitagliptin would be preferred over sulfonylurea would be £22,000/QALY (see figure 19).

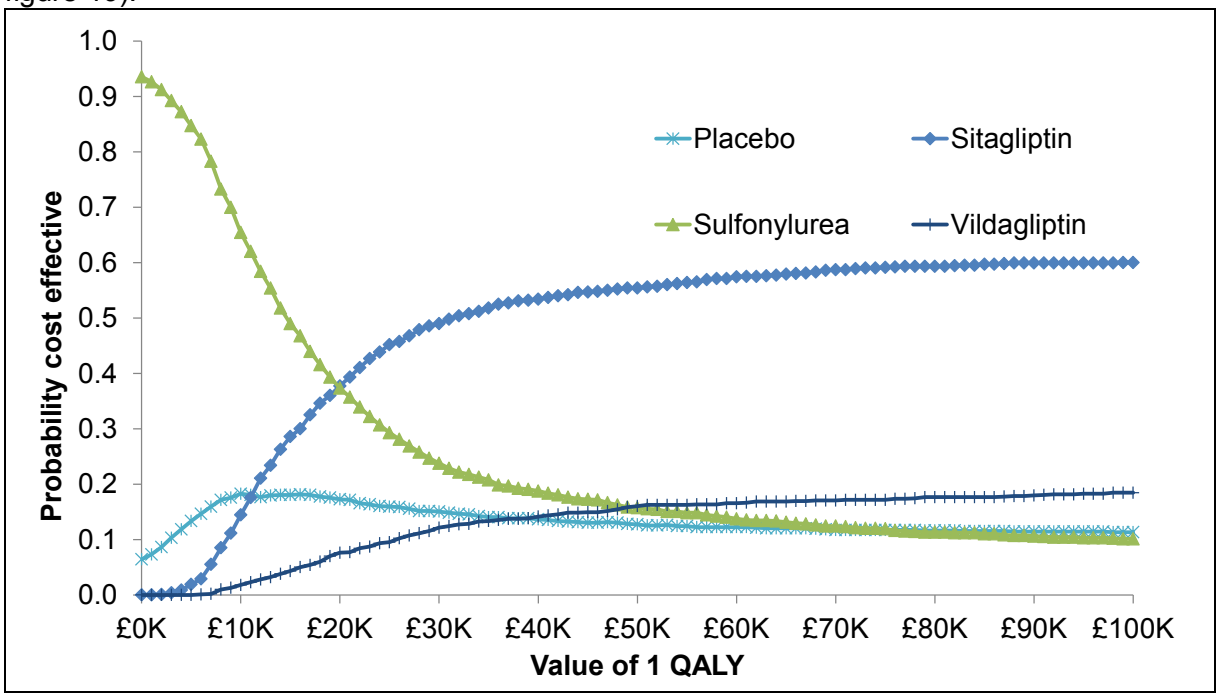


Figure 18: Cost-effectiveness acceptability curve for initial therapy when neither metformin, repaglinide nor pioglitazone are treatment options

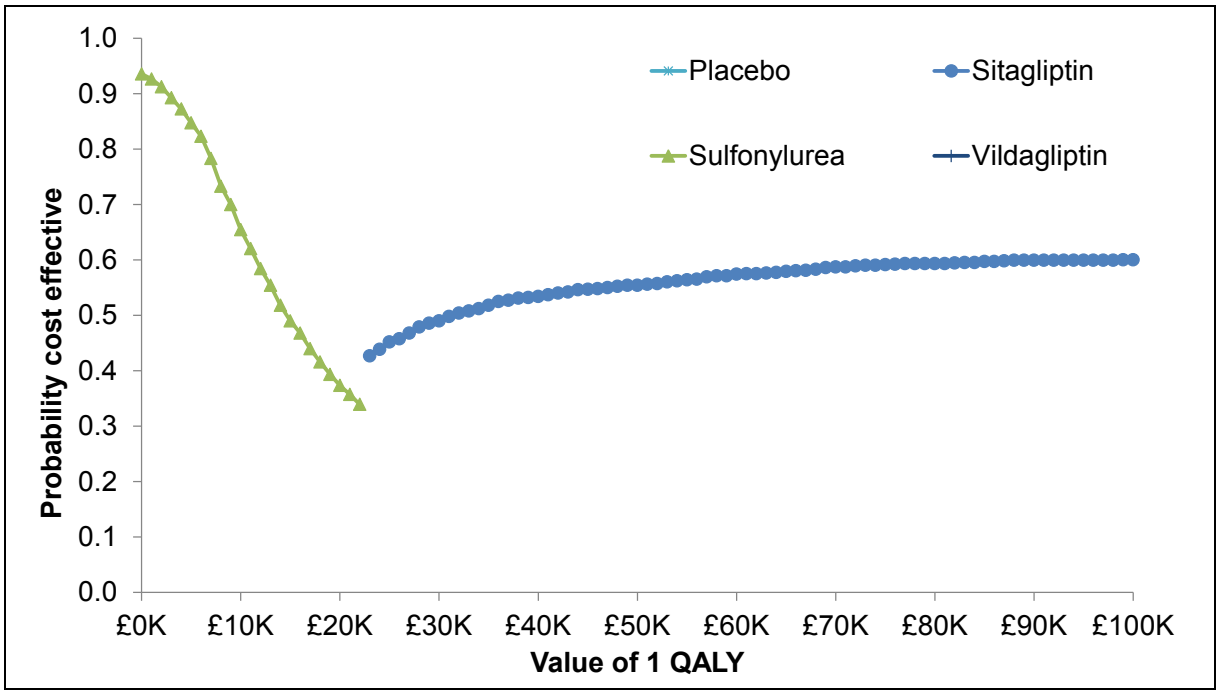
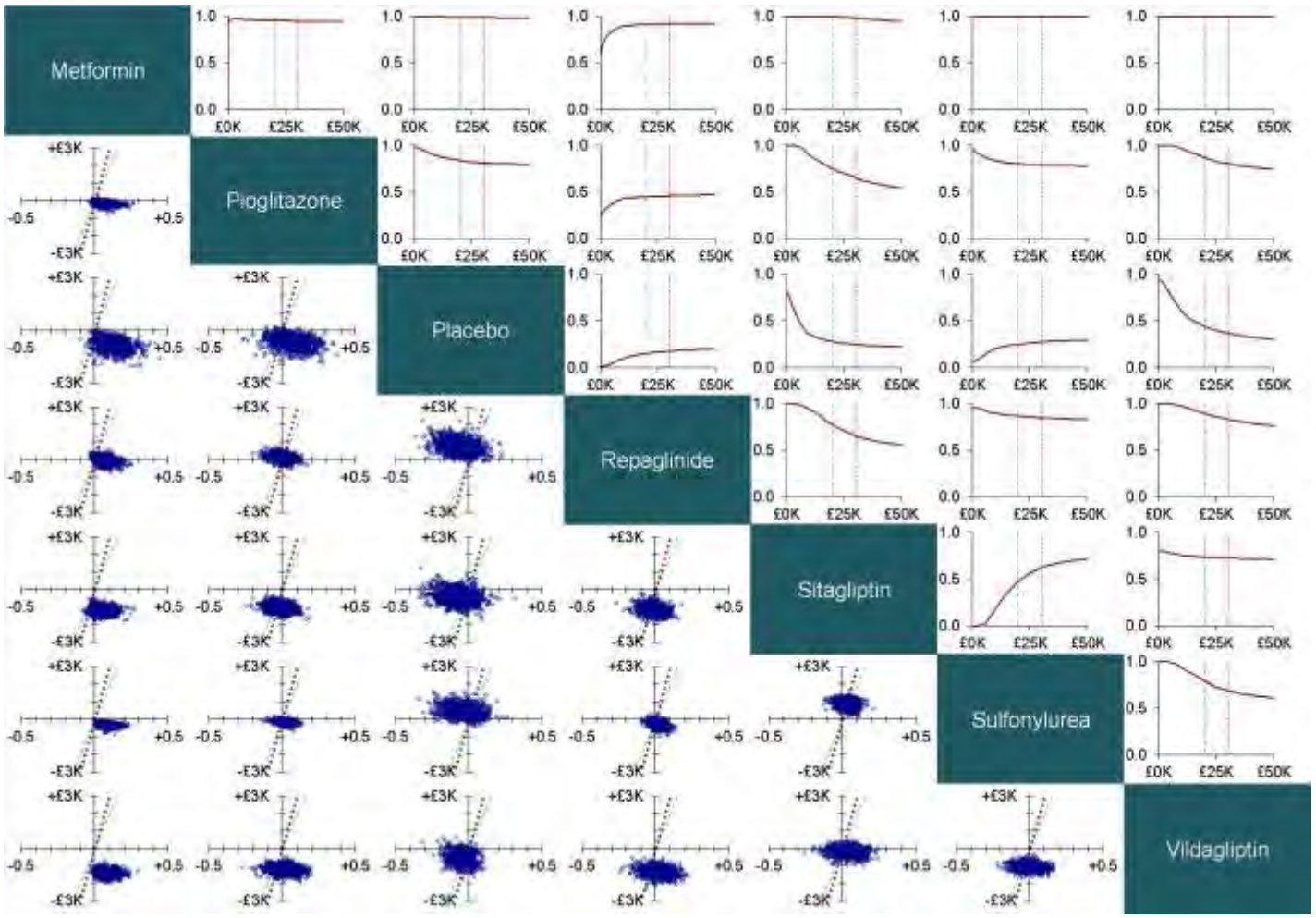


Figure 19: Cost-effectiveness acceptability frontier for initial therapy when neither metformin, repaglinide nor pioglitazone are treatment options

In order to further assess whether, given correlated treatment effects, there was correlation between treatment options in the PSA, pairwise treatment option were plotted, showing both

the cost-effectiveness plane results scatter and the CEAC for each combination with £20,000/QALY threshold marked in green dashes and £30,000/QALY marked in red dots (see figure 20). It can be seen that there is little difference between sitagliptin and sulfonylurea.



Lower-left segment shows incremental costs and QALYs from each iteration of the PSA for each pairwise comparison (option above versus option to the right); upper-right segment shows cost-effectiveness acceptability curve (probability that option to the left is more cost effective than option below, at increasing values of 1 QALY). In both types of graph, a maximum acceptable ICER of £20,000/QALY is indicated by a green dashed line and a maximum acceptable ICER of £30,000/QALY is indicated by a red dotted line.

Figure 20: Pairwise probabilistic comparisons of treatment options for initial therapy

4.3 Initial therapy – 1-way sensitivity analyses

A number of structural assumptions and inputs were indicated for 1-way sensitivity analyses (see 3.11.2).

4.3.1 Use of year-2 HbA1c and weight treatment-effect data

When we configured the model to use year-2 HbA1c and weight data wherever they were available, pioglitazone became the cheapest treatment option. This was driven by a particular large drop in HbA1c (−2.0%) which the GDG felt was unrealistic in clinical practice. However, metformin still benefitted from a greater weight-loss than any other treatment at year 2, which translated to gaining the most lifetime discounted QALYs and hence metformin had an ICER of £11,300/QALY compared with pioglitazone and remained the most cost-effective treatment option for initial therapy (see table 92).

When we removed metformin from the decision space, repaglinide was no longer the most cost-effective option and was dominated by pioglitazone (see table 93). This was due to the aforementioned HbA1c gains with pioglitazone, rather than a worsening of repaglinide as no year-2 data were available for repaglinide. As repaglinide is dominated, the results when neither metformin nor repaglinide are within the decision space did not change (table not shown). When neither metformin, repaglinide nor pioglitazone are within the decision space, sulfonylurea was the cheapest treatment option and sitagliptin had an ICER of £55,800/QALY compared with sulfonylurea (see table 94).

As all treatment options had year-1 data available, there was no need to analyse year-2 data only where it was additional to year-1 data (see table 71) as the results would be the same as for the base-case analysis.

Table 92: Initial therapy sensitivity analysis – year 2 data where available

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£18,784	9.063			
Metformin -> Met-SU -> Met-I(NPH)	£18,957	9.079	£173	0.015	£11,254
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,018	9.028	£61	-0.051	Dominated
Repaglinide -> Met-SU -> Met-I(NPH)	£19,167	9.004	£209	-0.074	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,739	8.953	£782	-0.126	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,214	9.049	£1257	-0.029	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,399	9.028	£1442	-0.051	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 93: Initial therapy when metformin was not within the decision space sensitivity analysis – year 2 data where available

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£18,784	9.063			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,018	9.028	£234	-0.035	Dominated
Repaglinide -> Met-SU -> Met-I(NPH)	£19,167	9.004	£382	-0.059	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,739	8.953	£955	-0.110	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,214	9.049	£1430	-0.014	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,399	9.028	£1615	-0.036	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 94: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – year 2 data where available

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,018	9.028			
Placebo -> Met-SU -> Met-I(NPH)	£19,739	8.953	£721	-0.075	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,214	9.049	£1196	0.021	£55,788
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,399	9.028	£185	-0.022	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

4.3.2 Alternative weight profiles

The base case model assumed that treatment-related weight-loss was regained after 1 year and treatment-related weight-gain remained forever (see 3.2.6). Two sensitivity analyses considered alternative weight profiles.

A sensitivity analysis with gradual weight-loss rebound favoured treatment options with evidence for treatment-related weight-loss by increasing their QALY gains. This analysis indicated that, whilst metformin still dominated the full initial therapy decision space (see table 95), the lower lifetime discounted QALY treatment-related weight-losses reduced the ICERs for non-dominated options (see table 96, table 97 and table 98). In particular, when neither metformin, repaglinide nor pioglitazone were within the decision space, the ICER for sitagliptin (compared with sulfonylurea) reduced from £21,200/QALY in the base case to £18,800 in the gradual weight rebound sensitivity analysis.

Table 95: Initial therapy sensitivity analysis – gradual weight rebound

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,437	9.064			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,458	9.016	£22	-0.048	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,602	9.008	£166	-0.057	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,762	8.987	£325	-0.077	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,247	8.950	£811	-0.114	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,594	9.032	£1158	-0.033	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,802	8.999	£1365	-0.066	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 96: Initial therapy when metformin was not within the decision space sensitivity analysis – gradual weight rebound

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,458	9.016			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,602	9.008	£144	-0.009	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,762	8.987	£303	-0.029	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,247	8.950	£789	-0.066	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,594	9.032	£1136	0.015	£74,590
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,802	8.999	£207	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 97: Initial therapy when metformin and repaglinide were not within the decision space sensitivity analysis – gradual weight rebound

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,602	9.008			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,762	8.987	£159	-0.020	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,247	8.950	£645	-0.057	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,594	9.032	£992	0.024	£41,395
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,802	8.999	£207	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea; Met-I(NPH): metformin-NPH insulin

Table 98: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – gradual weight rebound

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,762	8.987			
Placebo -> Met-SU -> Met-I(NPH)	£20,247	8.950	£486	-0.037	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,594	9.032	£833	0.044	£18,771
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,802	8.999	£207	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea; Met-I(NPH): metformin-NPH insulin

Alternatively, treatment-related weight-change could be assumed to only last for 1 year – this would be more in line with the evidence-limited base-case assumption for weight-loss and would reduce the lifetime discounted QALY losses for weight-gaining treatments. A sensitivity analysis where treatment-related weight-gain only lasted 1 year indicated that, in almost all situations, the least expensive treatment would be dominant (metformin or, if metformin is not an option, repaglinide or, if neither metformin nor repaglinide are options, pioglitazone). This result arises because the relative impact of the weight advantages of sitagliptin were reduced (see table 99, table 100 and table 101). Where neither metformin, repaglinide nor pioglitazone are options, sitaglitpin has an ICER of £86,200/QALY compared with sulfonylurea (see table 102)

Table 99: initial therapy sensitivity analysis – weight gained is lost after 1 year

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,364	9.060			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,383	9.051	£19	-0.008	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,542	9.048	£178	-0.012	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,682	9.032	£318	-0.028	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,171	8.976	£807	-0.084	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,525	9.042	£1161	-0.018	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,735	9.014	£1371	-0.045	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 100: Initial therapy when metformin was not within the decision space sensitivity analysis – weight gained is lost after 1 year

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,383	9.051			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,542	9.048	£159	-0.003	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,682	9.032	£299	-0.020	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,171	8.976	£788	-0.076	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,525	9.042	£1,142	-0.010	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,735	9.014	£1,352	-0.037	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 101: Initial therapy when metformin and repaglinide were not within the decision space sensitivity analysis – weight gained is lost after 1 year

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,542	9.048			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,682	9.032	£140	-0.016	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,171	8.976	£628	-0.072	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,525	9.042	£982	-0.006	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,735	9.014	£1193	-0.034	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 102: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – weight gained is lost after 1 year

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,682	9.032			
Placebo -> Met-SU -> Met-I(NPH)	£20,171	8.976	£489	-0.056	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,525	9.042	£843	0.010	£86,197
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,735	9.014	£210	-0.027	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

4.3.3 Assumed daily drug doses

Table 103: Initial therapy sensitivity analysis – assumed daily drug doses

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£18,950	9.035			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,003	8.991	£53	-0.044	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,098	8.981	£148	-0.054	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,261	8.961	£311	-0.075	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,692	8.925	£741	-0.111	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,292	9.004	£1342	-0.031	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,356	8.972	£1406	-0.064	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Using the assumed daily drug doses rather than those based on included studies reduced the lifetime discounted costs for each treatment option (due to metformin-NPH insulin being

cheaper), but did not alter the conclusions for initial therapy. In the full decision space, metformin remained dominant (see table 103) and, when metformin could not be taken, repaglinide was the most cost-effective option (see table 104). When neither metformin nor repaglinide could be taken, pioglitazone was the most cost effective option (see table 105) and when neither metformin, repaglinide nor pioglitazone were within the decision space, sitagliption had an ICER of £23,600/QALY compared with sulfonylurea (see table 106).

Table 104: Initial therapy when metformin was not within the decision space sensitivity analysis – assumed daily drug doses

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,003	8.991			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,098	8.981	£95	-0.009	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,261	8.961	£258	-0.030	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,692	8.925	£689	-0.066	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,292	9.004	£1289	0.014	£94,305
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,356	8.972	£64	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 105: Initial therapy when metformin and repaglinide were not within the decision space sensitivity analysis – assumed daily drug doses

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,098	8.981			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,261	8.961	£163	-0.021	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,692	8.925	£593	-0.057	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,292	9.004	£1194	0.023	£51,776
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,356	8.972	£64	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 106: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – assumed daily drug doses

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,261	8.961			
Placebo -> Met-SU -> Met-I(NPH)	£19,692	8.925	£431	-0.036	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,292	9.004	£1031	0.044	£23,581
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,356	8.972	£64	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

4.3.4 Baseline hypoglycaemia rates

When we halved baseline hypoglycaemia rates, lifetime discounted costs reduced (due to less serious hypoglycaemic episodes) and lifetime discounted QALYs increased (due to fewer QALYs lost from less symptomatic and serious hypoglycaemic episodes). Similarly, doubling baseline hypoglycaemia rates increased lifetime discounted costs and reduced lifetime discounted QALYs. However, metformin remained dominant in both sensitivity analyses (see table 107 and table 111).

In decision spaces with less treatment options, low baseline hypoglycaemia rates reduced the lifetime discounted QALY gains of sitagliptin over other treatment options (see table 108, table 109 and table 110) and similarly high baseline hypoglycaemia rates increased the

lifetime discounted QALY gains of sitagliptin over other treatment options (see table 112, table 113 and table 114). When neither metformin, repaglinide nor pioglitazone were within the decision space, both sulfonylurea and sitagliptin were cost-effective treatment options.

Table 107: Initial therapy sensitivity analysis – low baseline hypoglycaemia rates

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,127	9.033			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,138	8.991	£11	-0.041	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,293	8.979	£166	-0.054	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,437	8.962	£310	-0.071	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,931	8.922	£804	-0.111	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,276	9.001	£1149	-0.032	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,501	8.969	£1374	-0.063	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 108: Initial therapy when metformin was not within the decision space sensitivity analysis – low baseline hypoglycaemia rates

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,138	8.991			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,293	8.979	£155	-0.013	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,437	8.962	£299	-0.029	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,931	8.922	£793	-0.069	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,276	9.001	£1138	0.009	£120,507
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,501	8.969	£225	-0.031	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 109: Initial therapy when metformin and repaglinide were not within the decision space sensitivity analysis – low baseline hypoglycaemia rates

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,293	8.979			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,437	8.962	£144	-0.017	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,931	8.922	£638	-0.057	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,276	9.001	£983	0.022	£44,587
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,501	8.969	£225	-0.031	Dominated

(a) Met-SU:metformin-sulfonylurea then metformin-NPH insulin

Table 110: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – low baseline hypoglycaemia rates

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,437	8.962			
Placebo -> Met-SU -> Met-I(NPH)	£19,931	8.922	£494	-0.040	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,276	9.001	£839	0.039	£21,562
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,501	8.969	£225	-0.031	Dominated

(a) Met-SU:metformin-sulfonylurea then metformin-NPH insulin

Table 111: Initial therapy sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,239	9.020			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,277	8.966	£38	-0.054	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.967	£173	-0.053	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,579	8.935	£340	-0.085	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,046	8.911	£807	-0.109	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,396	8.991	£1156	-0.029	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,604	8.958	£1365	-0.062	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 112: Initial therapy when metformin was not within the decision space sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,277	8.966			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.967	£135	0.001	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,579	8.935	£302	-0.031	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,046	8.911	£769	-0.055	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,396	8.991	£1119	0.024	£45,933
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,604	8.958	£208	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 113: Initial therapy when metformin and repaglinide were not within the decision space sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.967			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,579	8.935	£167	-0.032	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,046	8.911	£634	-0.056	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,396	8.991	£984	0.024	£41,508
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,604	8.958	£208	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 114: Initial therapy when neither metformin, repaglinide nor pioglitazone were within the decision space sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,579	8.935			
Placebo -> Met-SU -> Met-I(NPH)	£20,046	8.911	£467	-0.024	Dominated
Sitagliptin-> Met-SU -> Met-I(NPH)	£20,396	8.991	£817	0.056	£14,658
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,604	8.958	£208	-0.033	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

4.3.5 Treatment effect adjustment for baseline HbA1c

When the original health economic model was run without the treatment effect adjustment for baseline HbA1c, the initial therapy incremental results were very similar to the base-case results (see table 115, table 116, table 117 and table 118). In the decision space excluding metformin, repaglinide and pioglitazone (table 118), sulfonylurea and sitagliptin were both acceptable treatment options.

Table 115: Initial therapy sensitivity analysis – no treatment effect adjustment for baseline HbA1c

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin -> Met-SU -> Met-I(NPH)	£19,072	9.064			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,122	9.016	£50	-0.047	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,255	9.010	£183	-0.054	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,388	8.990	£316	-0.073	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,572	8.971	£500	-0.093	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,352	9.035	£1280	-0.029	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,542	9.009	£1470	-0.055	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 116: Initial therapy sensitivity analysis when metformin was not within the decision space – no treatment effect adjustment for baseline HbA1c

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Repaglinide -> Met-SU -> Met-I(NPH)	£19,122	9.016			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,255	9.010	£133	-0.006	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,388	8.990	£266	-0.026	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,572	8.971	£450	-0.045	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,352	9.035	£1230	0.019	£65,359
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,542	9.009	£190	-0.026	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 117: Initial therapy sensitivity analysis when metformin and repaglinide were not within the decision space – no treatment effect adjustment for baseline HbA1c

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,255	9.010			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,388	8.990	£133	-0.020	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£19,572	8.971	£318	-0.039	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,352	9.035	£1097	0.025	£43,952
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,542	9.009	£190	-0.026	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

Table 118: Initial therapy sensitivity analysis when neither metformin, repaglinide nor pioglitazone were within the decision space – no treatment effect adjustment for baseline HbA1c

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,388	8.990			
Placebo -> Met-SU -> Met-I(NPH)	£19,572	8.971	£185	-0.019	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,352	9.035	£964	0.045	£21,481
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,542	9.009	£190	-0.026	Dominated

(a) Met-SU: metformin-sulfonylurea then metformin-NPH insulin

4.4 Initial therapy – discussion and conclusions

It was clear that the most cost-effective initial therapy treatment option modelled for the pharmacological lowering of blood glucose in people with type 2 diabetes was metformin. Metformin dominated other treatment options in the base-case analysis and was the most cost-effective option at a maximum acceptable ICER of £20,000/QALY in 88% of probabilistic iterations. In the only sensitivity analysis where metformin was not dominant (using 2-year HbA1c data), it had an ICER of £11,300/QALY. The GDG were not convinced of the validity of the clinical outcome estimates that drove this sensitivity analysis.

When people with type 2 diabetes could not take metformin, repaglinide was the most cost-effective initial therapy treatment option, dominating all other treatment options with the exception of sitagliptin (ICER £73,300/QALY) and the most cost-effective of the 6 treatment options at a maximum acceptable ICER of £20,000/QALY in 45% of probabilistic iterations. In sensitivity analyses, the ICER for sitagliptin compared with repaglinide varied from £45,900/QALY to dominated.

However, there were no first intensification treatment options including repaglinide and the GDG were concerned that it would not be clinically feasible or appealing to people to start initial therapy on repaglinide and then to have to change to 2 different drugs at first intensification.

When people cannot or choose not to take metformin or repaglinide, pioglitazone was the cheapest initial therapy treatment option. The base case ICER for sitagliptin compared with pioglitazone was above a maximum acceptable ICER of £20,000/QALY (£62,500/QALY); with the exception of the 2-year data sensitivity analysis (where pioglitazone dominated other treatment options), the ICER for sitagliptin compared with sulfonylurea ranged from £41,100/QALY to dominated. Pioglitazone (most cost-effective in 60% of iterations) and sitagliptin (most cost-effective in 18% of iterations) were the most cost-effective treatment options at a maximum acceptable ICER of £20,000/QALY.

The GDG expressed reservations about the number of people (albeit in a small subgroup of people who cannot or choose not to take metformin or repaglinide) for whom pioglitazone would be contra-indicated and therefore considered a decision space containing only the 4 remaining treatment options (placebo, sitagliptin, sulfonylurea and vildagliptin). In the base-case analysis, sitagliptin had an ICER of £22,300 compared with sulfonylurea. Whilst in sensitivity analyses this ICER varied between £14,700/QALY and £86,200/QALY, sitagliptin was the most cost effective treatment option in 38% of PSA iterations, compared with 37% for sulfonylurea. The GDG were happy for either sitagliptin or sulfonylurea to be recommended for people with type 2 diabetes who could not take metformin, repaglinide or piogitazone.

The GDG also noted the model did not account for any potential long-term adverse events or safety concerns associated with thiazolidinediones or DPP-4 inhibitors that could alter the cost-effectiveness conclusions. No health economic models of diabetes currently include such concerns. Equally, no health economic models consider any longer-term benefits of metformin on factors other than HbA1c.

In none of the base-case analyses was sulfonylurea – the currently recommended alternative to metformin – a cost-effective treatment option. However, it should be noted that no previous UK CUA for initial therapy was found (see 2.2.1). Also, the original health economic model used HbA1c treatment effect data at 1 year – the clinical review found that sulfonylurea (and repaglinide) was more effective at shorter time periods, but effects were not sustained at 1 year (see section 8.4.4.3 in the main guideline). In contrast, the economic model did reflect the low rankings at 1 year for hypoglycaemia and body weight for these treatments. Sulfonylurea may have a role in short-term HbA1c reduction, but was not cost effective compared with other treatment options for periods of 1 year or longer. Individual preference for rapid HbA1c reduction compared with weight-changes would need to be carefully considered.

Using an assumed daily dose had a slight impact on the cost effectiveness results, but doing so broke the link between treatment effect magnitude and drug dose required to achieve such an effect.

Differences between treatment options at initial therapy were small, due to the normalising effect of future intensifications in the economic model – people were only on their initial therapies for an average of 3.4 years. Lifetime discounted QALY differences between the best (metformin) and worst (placebo) treatments in the base case were small – less than 46 quality adjusted life days out of 9.0 remaining QALYs. Cost differences were largely due to the costs of the drugs themselves.

Sensitivity analyses indicated that the cost-effectiveness results were somewhat sensitive to model structure and parameters related to treatment-related weight-change and hypoglycaemia. These were short-term outcomes where discounting has little influence, whereas much of the modelling and computer processing of this and other type 2 diabetes health economic models is aimed at predicting long-term outcomes, for which the effects of discounting become more pronounced.

The choice of weight profile had the largest influence on the cost-effectiveness results. In the base case, the GDG chose a conservative weight profile they felt best reflected the evidence and their clinical experience. Further research to evidence longer-term weight profiles would help to remove uncertainty from future type 2 diabetes modelling.

4.5 First intensification – base-case results

When averaged across all 7 modelled therapies, the simulated cohort starting on first intensification therapy survived for an average of 16.3 undiscounted life years – given an average starting age of 62.7, people survived until an average age of 79.0 years. Irrespective of first intensification therapy, people intensified to metformin-NPH insulin when each simulated individual's HbA1c rose to a value greater than 7.5%.

As a consequence of the gradual progression of type 2 diabetes and modelled HbA1c progression, after 12 years no individuals remained on first intensification therapy. By year 5, less than 30% of people remained on first intensification therapy (see table 119). People were on first intensification therapy for an average of 3.7 years before intensifying therapy. The intensification of the metformin-sulfonylurea cohort (as an example as it was thought to be the most commonly used existing first intensification therapy) can be seen in figure 21.

Table 119: First intensification – people on each therapy level by year

Year	First Intensification	Second Intensification	Dead
1	98.8%	0.0%	1.2%
2	81.3%	15.0%	3.6%
3	68.1%	25.6%	6.3%
4	49.2%	41.7%	9.1%
5	29.7%	58.2%	12.1%
6	15.1%	69.6%	15.3%
7	6.6%	74.9%	18.5%
8	2.2%	75.9%	21.8%
9	0.5%	74.3%	25.3%
10	0.1%	71.2%	28.7%
...			

(a) Years 11 onwards not shown

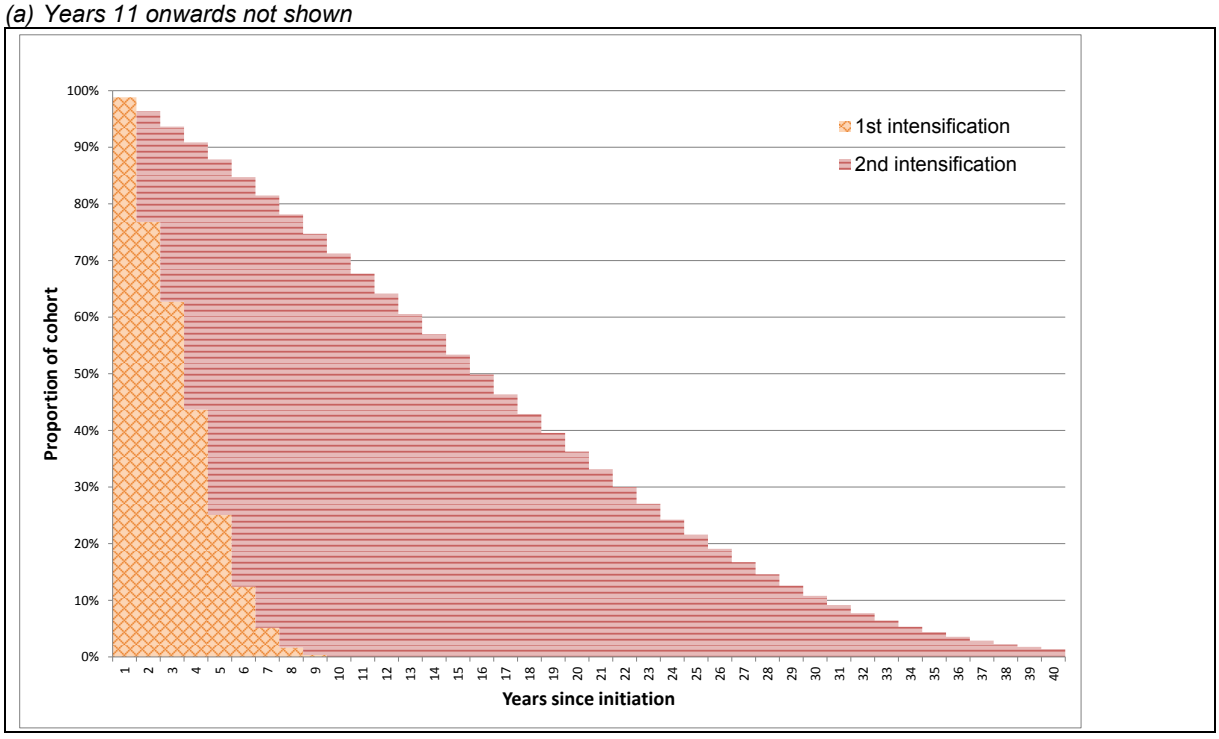


Figure 21: Years spent on each therapy level (metformin-sulfonylurea)

4.5.1 Clinical outcomes

As for initial therapy, there was very little difference in mean lifetime complication rates between treatments (see table 120). The normalising effect of treatment intensification still played a role, but the lack of significant differences between HbA1c treatment effects had a greater impact.

Table 120: Mean lifetime event rates for first intensification of therapy

Treatment	Amputation	Blindness	Renal Failure	CHF	IHD	MI	Stroke	Life Years
Metformin-Sitagliptin	0.03679	0.07193	0.02654	0.15279	0.11499	0.33379	0.14703	16.275
Exenatide-Metformin	0.03684	0.07203	0.02656	0.15308	0.11500	0.33395	0.14713	16.276
Linagliptin-Metformin	0.03718	0.07245	0.02653	0.15356	0.11532	0.33497	0.14758	16.281
Metformin-Vildagliptin	0.03693	0.07203	0.02654	0.15302	0.11506	0.33410	0.14712	16.285
Metformin-Sulfonylurea	0.03721	0.07245	0.02653	0.15344	0.11527	0.33490	0.14767	16.289
Metformin-Pioglitazone	0.03663	0.07169	0.02649	0.15254	0.11471	0.33323	0.14681	16.292
Liraglutide-Metformin	0.03703	0.07220	0.02650	0.15322	0.11513	0.33454	0.14739	16.296

(a) Results shown are from a single base case model run of 50,000 people through 1000 loops
(b) All treatments intensified to metformin-NPH insulin
(c) Event rates and life years are undiscounted
(d) CHF: congestive heart failure; IHD: ischaemic heart disease; MI: myocardial infarction
(e) For definitions of events, see Appendix F.2 of this document

4.5.2 Lifetime discounted QALYs

People who started the original health economic model at first intensification gained around 8.2 discounted QALYs (see table 121). The differences between treatments were driven mainly by differences in lifetime discounted QALYs losses due to weight-change, with smaller differences due to hypoglycaemic episodes.

The GLP-1 agonist-metformin treatment options (exenatide and liraglutide) gained most lifetime discounted QALYs, whilst metformin-pioglitazone and metformin-sulfonylurea gained the fewest lifetime discounted QALYs. The differences in lifetime discounted QALY gains were primarily driven by differences in weight-change.

Table 121: Mean lifetime discounted QALYs for first intensification of therapy

Treatment	UKPDS	Hypoglycaemia		Weight	Treatment switches	Total
		Symptomatic	Severe			
Metformin-pioglitazone	8.901	-0.297	-0.025	-0.363	-0.001	8.217
Metformin-sulfonylurea	8.903	-0.279	-0.024	-0.377	-0.001	8.223
Metformin-sitagliptin	8.893	-0.292	-0.025	-0.328	-0.001	8.247
Metformin-vildagliptin	8.899	-0.287	-0.024	-0.333	-0.001	8.254
Linagliptin-metformin	8.897	-0.288	-0.024	-0.328	-0.001	8.256
Exenatide-metformin	8.893	-0.295	-0.025	-0.315	-0.001	8.258
Liraglutide-metformin	8.906	-0.280	-0.024	-0.315	-0.001	8.286

(a) All treatments intensified to metformin-NPH insulin
(b) (b) UKPDS: QALYs gained within UKPDS OM1 as a result of survival and long term complications

4.5.3 Lifetime discounted costs

Again, UKPDS OM1-modelled complications accounted for the biggest proportion (between 59% and 68%) of lifetime discounted costs (see table 122). Compared with initial therapy, the lower proportion of lifetime discounted costs was due to increased therapy costs at first intensification and to shorter life years on more expensive second intensification therapy.

Treatment costs were the source of most variation in lifetime discounted costs. Metformin - pioglitazone and metformin-sulfonylurea incurred the lowest lifetime discounted costs, whilst the GLP-1 agonist-metformin options (exenatide and liraglutide) incurred the highest lifetime discounted costs.

Table 122: Mean lifetime discounted costs for first intensification of therapy

Treatment	UKPDS	Treatment Costs	Severe Hypoglycaemia	Treatment switches	Total
Metformin-pioglitazone	£14,052	£5660	£806	£6	£20,525
Metformin-sulfonylurea	£14,055	£5758	£835	£6	£20,653
Metformin-vildagliptin	£14,062	£6816	£824	£6	£21,708
Linagliptin-metformin	£14,062	£6889	£831	£6	£21,787
Metformin-sitagliptin	£14,069	£6902	£843	£7	£21,820
Exenatide-metformin	£14,072	£8447	£851	£8	£23,378
Liraglutide-metformin	£14,048	£8947	£806	£11	£23,812

(a) (a) All treatments intensified to metformin-NPH insulin
(b) (b) UKPDS: QALYs gained within UKPDS OM1 as a result of survival and long term complications

4.5.4 Incremental cost–utility results

Metformin-pioglitazone had the lowest lifetime discounted costs; metformin-sulfonylurea had very similar lifetime discounted costs and QALYs but was dominated by metformin-pioglitazone (see table 123).

The DPP-4-inhibitor-metformin treatment options (linagliptin, sitagliptin or vildagliptin) all produced very similar lifetime discounted costs and QALYs. The GDG were happy to consider these interventions to be similar enough to each other and consider the possibility of a class effect for these treatment options (see figure 22). Compared with metformin-pioglitazone, linagliptin-metformin had an ICER of £36,800/QALY.

Although the model estimates that GLP-1 agonist-metformin combinations are the most effective of the simulated regimens, the marginal QALY gains are insufficient to outweigh the additional costs these strategies incur. The model estimates high ICERs in excess of £60,000/QALY for these regimens.

Table 123: Mean lifetime incremental cost–utility results for first intensification

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,390	8.217			
Metformin-sulfonylurea -> Met-I(NPH)	£20,522	8.213	£132	-0.004	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,569	8.249	£1179	0.031	Ext. dom.
Linagliptin-metformin -> Met-I(NPH)	£21,654	8.252	£1264	0.034	£36,788
Metformin-sitagliptin -> Met-I(NPH)	£21,685	8.243	£31	-0.009	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,213	8.255	£1560	0.003	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,614	8.284	£1960	0.032	£61,381

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom: extendedly dominated

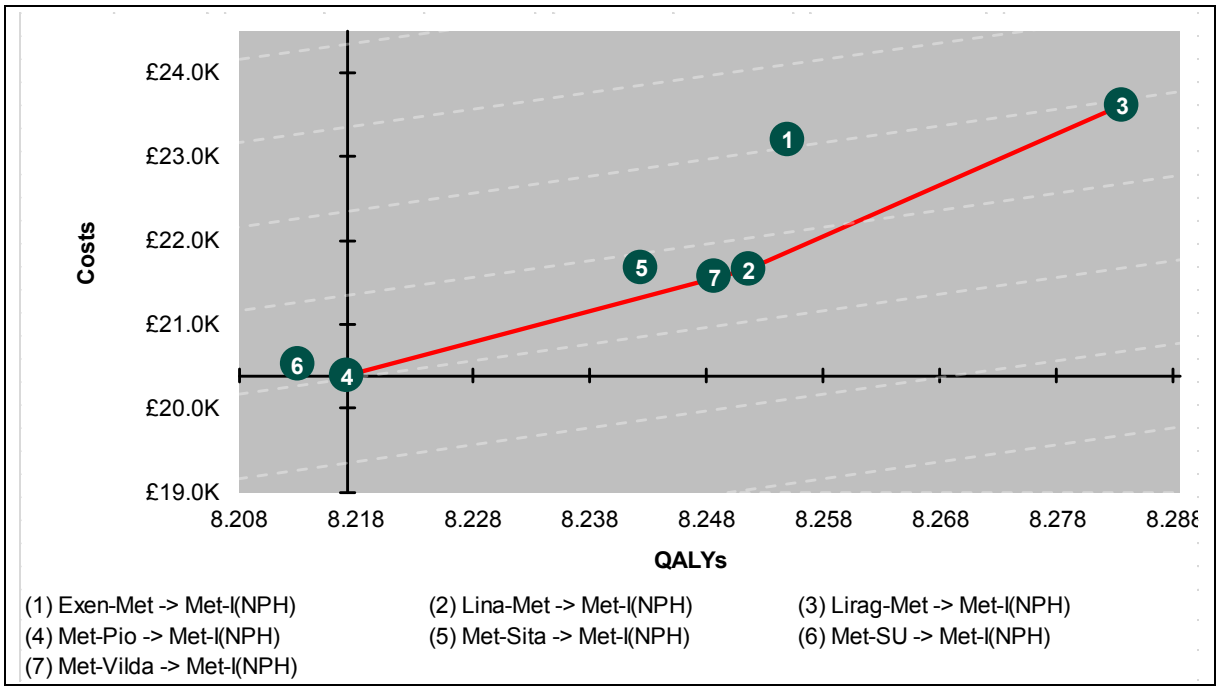


Figure 22: Cost–utility plane of mean lifetime results for first intensification

If pioglitazone is contra-indicated, metformin-sulfonylurea would be the cheapest and most cost-effective treatment option, as the ICER for linagliptin-metformin was £29,300/QALY compared with metformin-sulfonylurea (see table 124).

Table 124: Mean lifetime incremental cost–utility results for first intensification when metformin-pioglitazone was not in the decision space

			Incremental		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Metformin-sulfonylurea -> Met-I(NPH)	£20,522	8.213			
Metformin-vildagliptin -> Met-I(NPH)	£21,569	8.249	£1047	0.036	Ext. dom.
Linagliptin-metformin -> Met-I(NPH)	£21,654	8.252	£1132	0.039	£29,312
Metformin-sitagliptin -> Met-I(NPH)	£21,685	8.243	£31	-0.009	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,213	8.255	£1560	0.003	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,614	8.284	£1960	0.032	£61,381

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom: extendedly dominated

Table 125: Mean lifetime incremental cost–utility results for first intensification when metformin-pioglitazone and metformin-sulfonylurea were not in the decision space

			Incremental		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Metformin-vildagliptin -> Met-I(NPH)	£21,569	8.249			
Linagliptin-metformin -> Met-I(NPH)	£21,654	8.252	£85	0.003	£29,154
Metformin-sitagliptin -> Met-I(NPH)	£21,685	8.243	£31	-0.009	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,213	8.255	£1560	0.003	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,614	8.284	£1960	0.032	£61,381

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom: extendedly dominated

The GDG wished to consider the most cost-effective option when metformin-pioglitazone and metformin-sulfonylurea were not within the decision space. Metformin-vildagliptin had the lowest lifetime discounted costs; linagliptin-metformin and metformin-sitagliptin had very similar lifetime discounted costs (see table 125).

No original health economic results could be provided for treatment options that did not involve metformin, due to absence of data with which to populate the model.

4.6 First intensification – probabilistic sensitivity analyses

At first intensification, metformin-pioglitazone was the most cost-effective treatment option at a maximum acceptable ICER of £20,000/QALY in 48% of 1000 PSA iterations. Metformin-sulfonylurea was the most cost-effective treatment in 19% of iterations (see figure 23). Also, the CEAF for first intensification showed the point at which linagliptin-metformin was the preferred treatment option was £37,000/QALY (see figure 24).

While metformin-pioglitazone and metformin-sulfonylurea showed only small incremental differences in the base case (see figure 22), the superiority of metformin-pioglitazone was maintained in most probabilistic iterations (metformin-sulfonylurea was the most cost-effective option at a maximum acceptable ICER of £20,000/QALY in less than 20% of iterations).

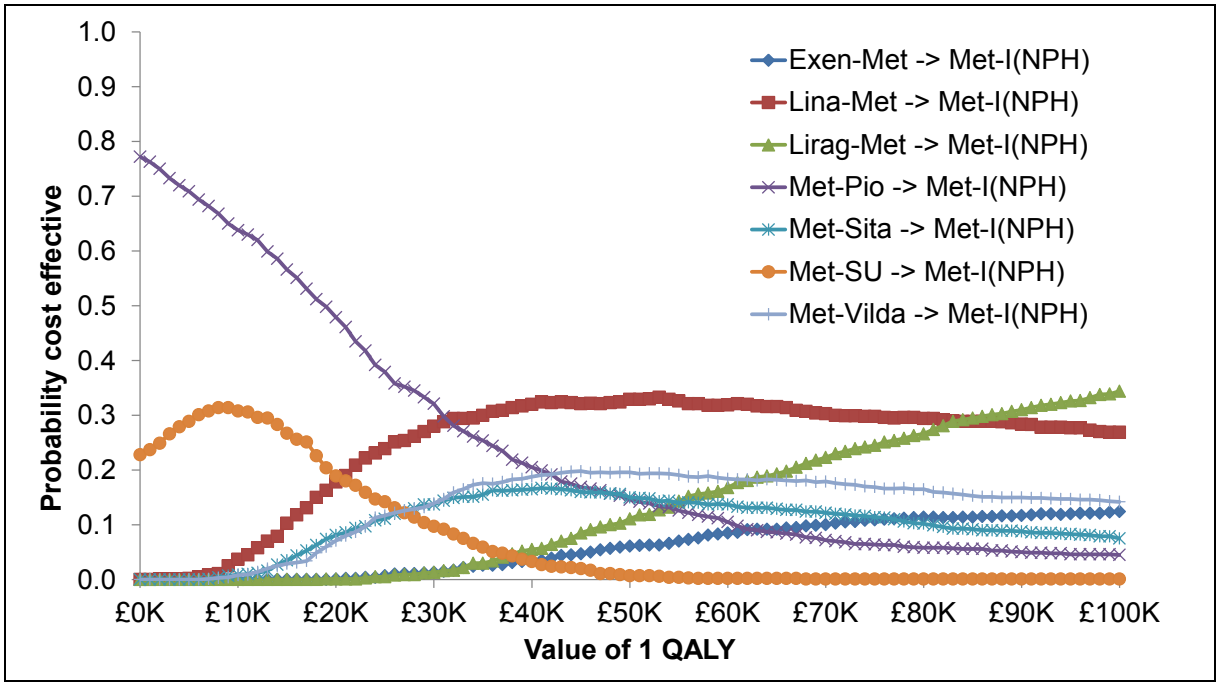


Figure 23: Cost-effectiveness acceptability curve for first intensification

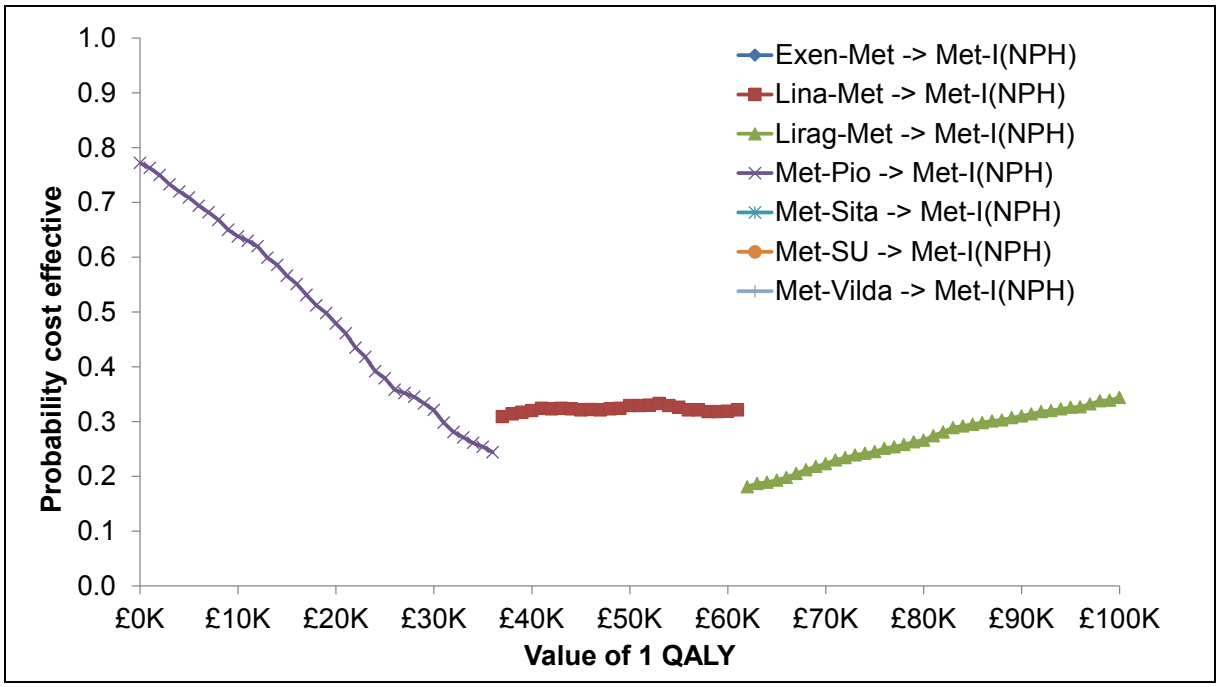


Figure 24: Cost-effectiveness acceptability frontier for first intensification

When metformin-pioglitazone and metformin-sulfonylurea were not within the decision space, it was reasonable to suggest that either linagliptin, vildagliptin or sitagliptin would be acceptable treatment options (see figure 25).

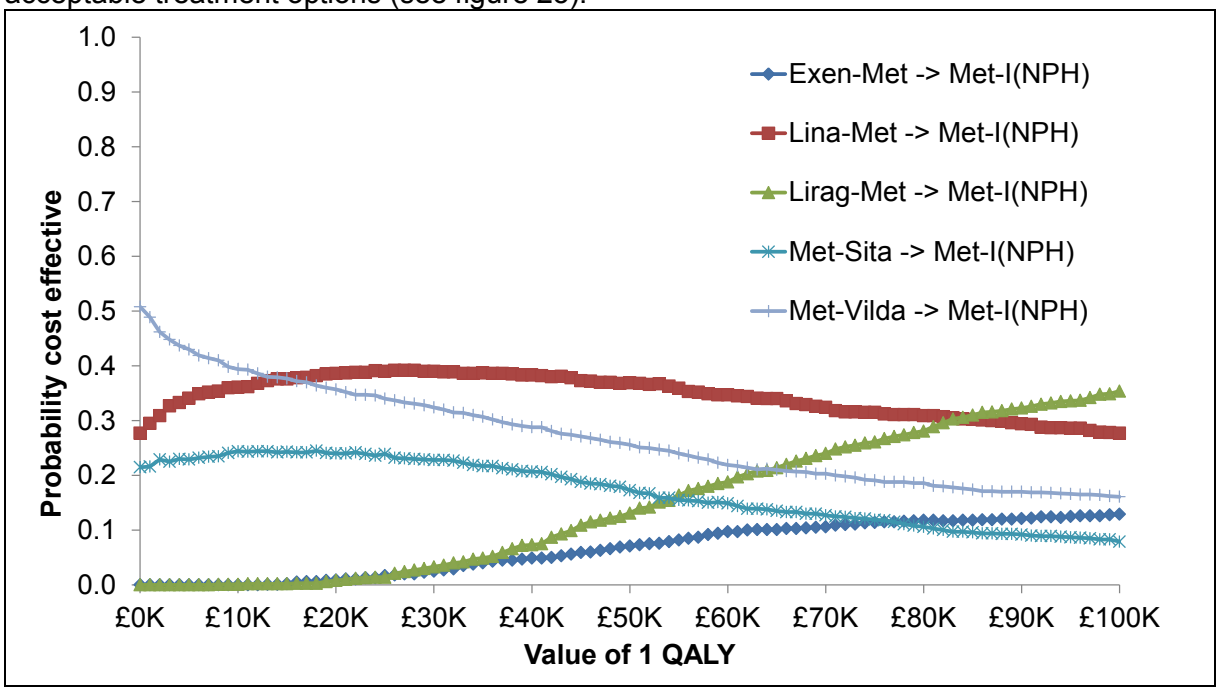
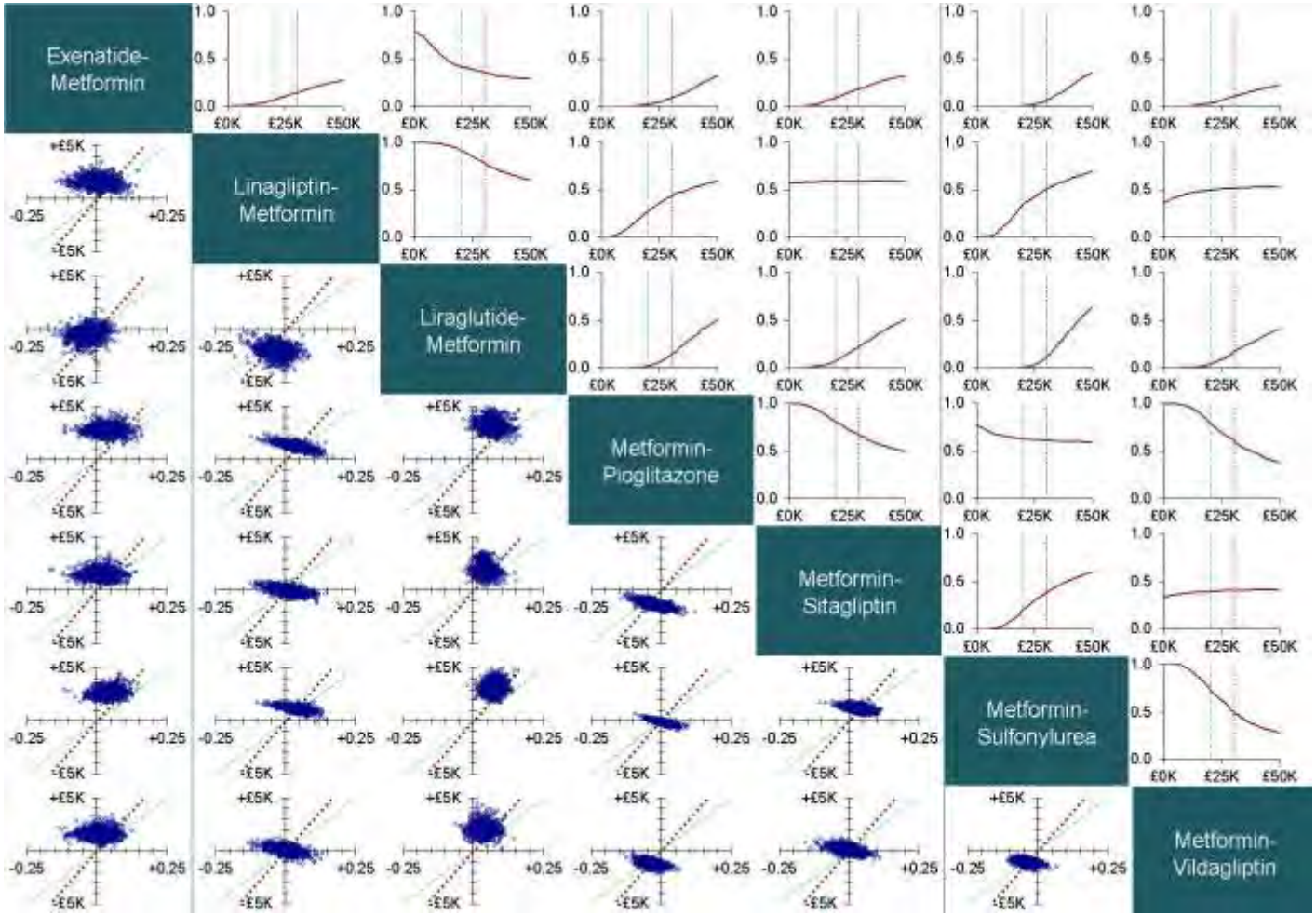


Figure 25: Cost-effectiveness acceptability curve for first intensification when metformin-pioglitazone and metformin-sulfonylurea were not within the decision space

In order to further assess whether, given correlated treatment effects, there was correlation between treatment options in the PSA, pairwise treatment option were plotted, showing both the cost-effectiveness plane results scatter and the CEAC for each combination with £20,000/QALY threshold marked in green dashes and £30,000/QALY marked in red dots (see figure 26). One of the features that is apparent in the pairwise analysis is the relatively

small differences between the 3 modelled DPP-4 inhibitors (each combined with metformin). When QALYs are assumed to have a value of £20,000, the probability that any of these options is superior to any other is within the range 0.4–0.6.



Lower-left segment shows incremental costs and QALYs from each iteration of the PSA for each pairwise comparison (option above versus option to the right); upper-right segment shows cost-effectiveness acceptability curve (probability that option to the left is more cost effective than option below, at increasing values of 1 QALY). In both types of graph, a maximum acceptable ICER of £20,000/QALY is indicated by a green dashed line and a maximum acceptable ICER of £30,000/QALY is indicated by a red dotted line.

Figure 26: Pairwise probabilistic comparisons of treatment options for first intensification of therapy

4.7 First intensification – 1-way sensitivity analyses

A number of structural assumptions and inputs were indicated for 1-way sensitivity analyses (see 3.11.2).

4.7.1 Use of year 2 HbA1c and weight treatment effect data

At first intensification, the use of year-2 HbA1c and weight data introduced 3 new treatments to the decision space (metformin-nateglinide, metformin-saxagliptin and pioglitazone-sulfonylurea).

When we configured the model to use year-2 HbA1c and weight data wherever they were available, metformin-pioglitazone remained the cheapest first intensification treatment option and the GLP-1 agonist-metformin treatment options (exenatide, liraglutide) remained the most costly treatment options (see table 126). Metformin-saxagliptin became the most cost-effective DPP-4 inhibitor-metformin treatment option, with an ICER of £28,400/QALY. However, all DPP-4 inhibitor-metformin treatment options again showed similar results (see figure 27). Metformin-vildagliptin showed lower lifetime discounted QALYs gained due to less weight-loss (less than 1 kg, versus around 2 kg for linagliptin-metformin and metformin-saxagliptin, see table 77).

Metformin-nateglinide was very similar to the DPP-4 inhibitor-metformin combinations, but was extendedly dominated by metformin-saxagliptin and metformin-pioglitazone. Pioglitazone-sulfonylurea was clearly not cost-effective compared with any metformin-containing regimens, due to high lifetime discounted QALY losses from treatment-related weight-gain (5.8 kg at year 2, see table 77).

When year-2 HbA1c and weight data were used only in addition to year 1 data, results were similar (see table 127). The ICER for metformin-saxagliptin compared with metformin-sulfonylurea and was £28,000/QALY (see figure 28).

Table 126: First intensification sensitivity analysis – year 2 data used where available

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,026	8.276			
Metformin-sulfonylurea -> Met-I(NPH)	£20,225	8.268	£199	-0.008	Dominated
Pioglitazone-sulfonylurea -> Met-I(NPH)	£20,269	8.178	£242	-0.099	Dominated
Metformin-nateglinide -> Met-I(NPH)	£21,005	8.296	£979	0.020	Ext. dom.
Metformin-saxagliptin -> Met-I(NPH)	£21,351	8.323	£1325	0.047	£28,352
Metformin-sitagliptin -> Met-I(NPH)	£21,457	8.313	£106	-0.010	Dominated
Linagliptin-metformin -> Met-I(NPH)	£21,467	8.308	£116	-0.015	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,521	8.272	£170	-0.051	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,188	8.277	£1836	-0.046	Dominated
Liraglutide-metformin -> Met-I(NPH)	£23,790	8.331	£2439	0.008	£290,955

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom.: extendedly dominated

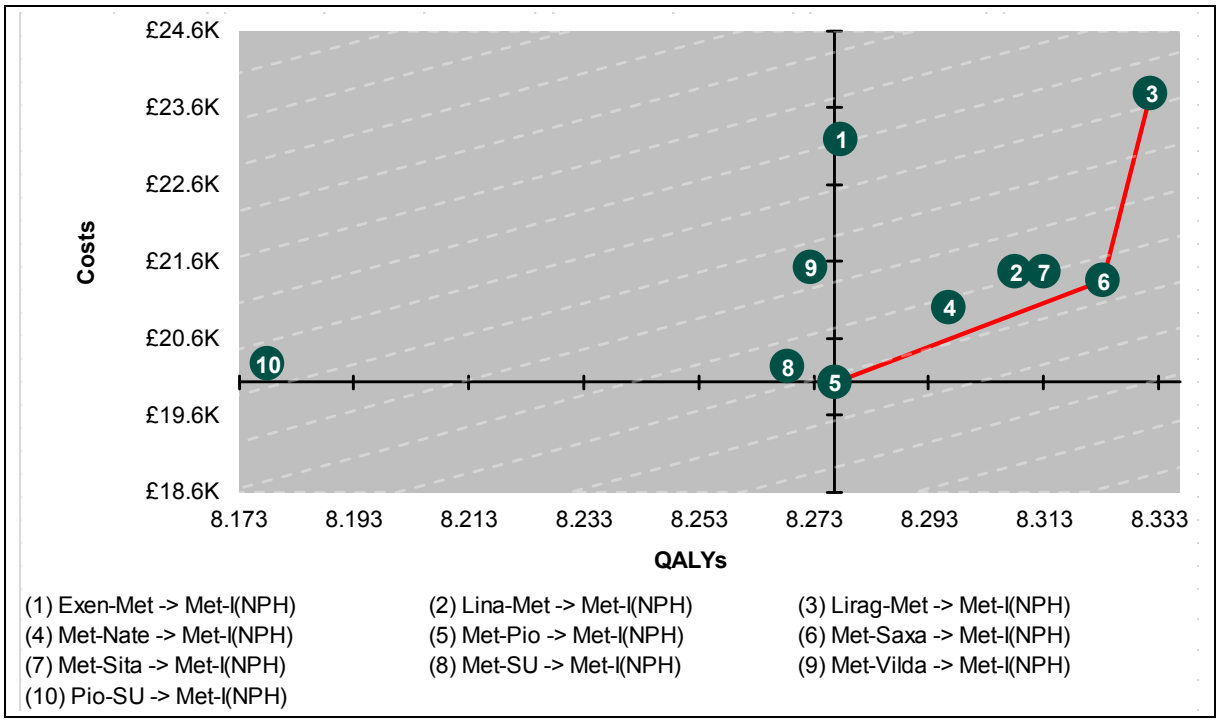


Figure 27: Cost–utility plane for first intensification sensitivity analysis – year 2 data where available

Table 127: First intensification sensitivity analysis – year 2 data used in addition to year 1 data

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£19,720	8.243			
Metformin-sulfonylurea -> Met-I(NPH)	£19,930	8.246	£210	0.003	Ext. dom.
Pioglitazone-sulfonylurea -> Met-I(NPH)	£19,984	8.146	£263	-0.097	Dominated
Metformin-nateglinide -> Met-I(NPH)	£20,722	8.263	£1001	0.020	Ext. dom.
Metformin-saxagliptin -> Met-I(NPH)	£21,065	8.291	£1345	0.048	£27,975
Metformin-sitagliptin -> Met-I(NPH)	£21,151	8.285	£86	-0.007	Dominated
Linagliptin-metformin -> Met-I(NPH)	£21,167	8.283	£101	-0.008	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,224	8.245	£158	-0.046	Dominated
Exenatide-metformin -> Met-I(NPH)	£22,895	8.246	£1830	-0.045	Dominated
Liraglutide-metformin -> Met-I(NPH)	£23,495	8.308	£2430	0.017	£142,352

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom.: extendedly dominated

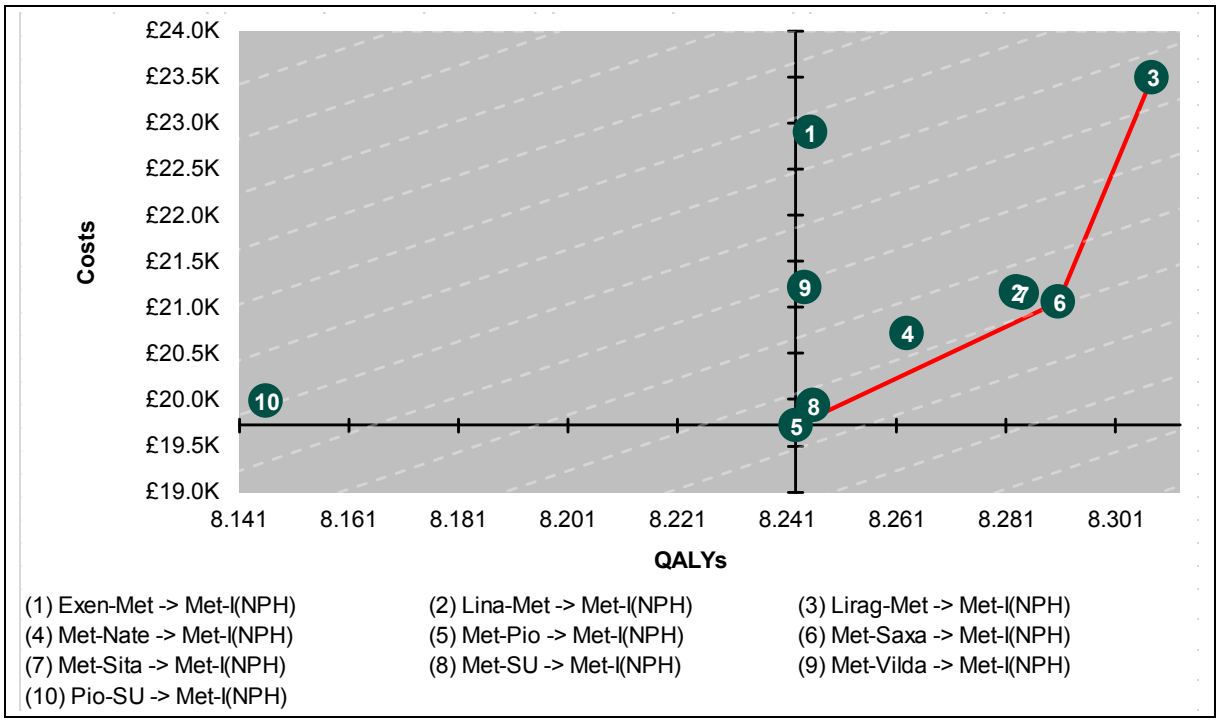


Figure 28: Cost–utility plane for first intensification sensitivity analysis – year 2 data used in addition to year 1 data

4.7.2 Alternative weight profiles

As for initial therapy, we undertook 2 sensitivity analyses with different weight profile assumptions. Under the assumption of gradual weight-loss rebound, the ICERs for treatments exhibiting treatment-related weight-loss were reduced. Metformin-vildagliptin became the cheapest DPP-4 inhibitor-metformin treatment option (ICER £32,500) compared with metformin-pioglitazone (see table 128) but, like in the base case, all the DPP-4 inhibitor-metformin treatment options produced very similar lifetime discounts costs and QALYs (see figure 29).

Table 128: First intensification sensitivity analysis – gradual weight rebound

			Incremental		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Metformin-pioglitazone -> Met-I(NPH)	£20,229	8.211			
Metformin-sulfonylurea -> Met-I(NPH)	£20,380	8.211	£151	0.000	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,411	8.248	£1182	0.036	£32,453
Linagliptin-metformin -> Met-I(NPH)	£21,492	8.250	£81	0.002	£40,695
Metformin-sitagliptin -> Met-I(NPH)	£21,534	8.239	£42	-0.011	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,071	8.251	£1580	0.002	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,584	8.281	£2092	0.031	£67,803

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom.: extendedly dominated

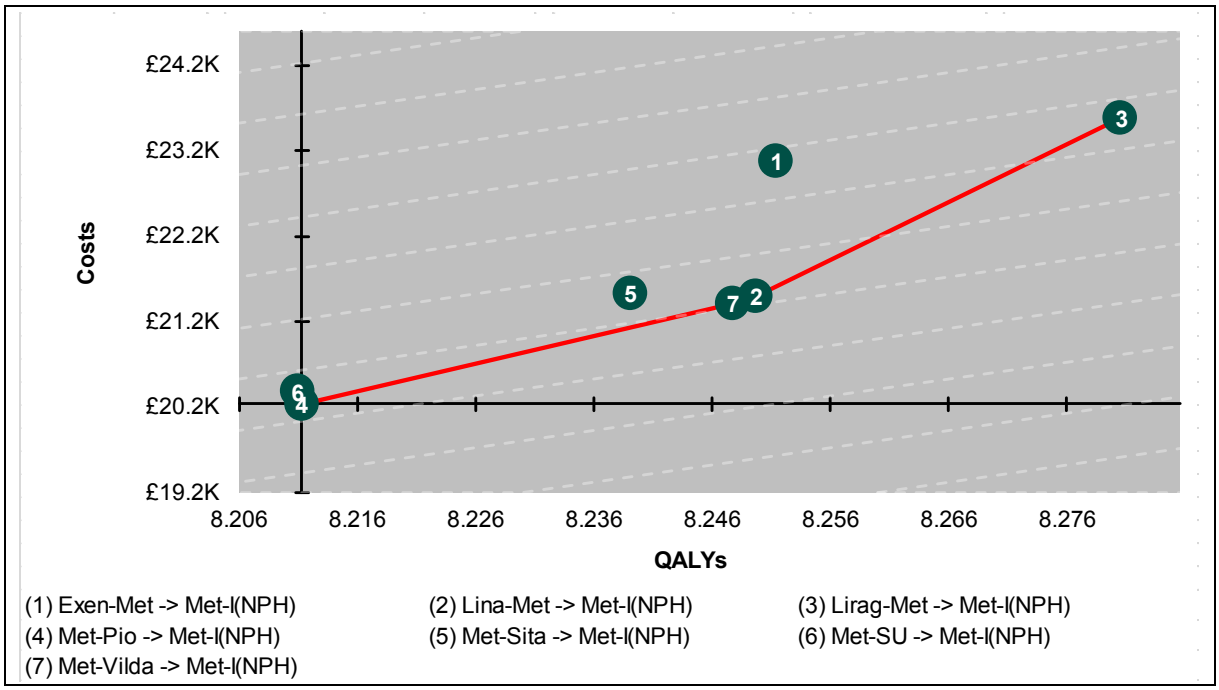


Figure 29: Cost–utility plane for first intensification sensitivity analysis – gradual weight rebound

Where treatment related weight change only lasts for 1 year for both weight lost and weight gained, weight gaining treatments lose fewer lifetime discounted QALYs. Metformin-pioglitazone was the first intensification treatment option that gained the most weight so when the negative QALY impact of weight gain was reduced in this sensitivity analysis, metformin-pioglitazone dominated most other treatment options (see table 129).

Table 129: First intensification sensitivity analysis –weight gained is lost after 1 year

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,428	8.284			
Metformin-sulfonylurea -> Met-I(NPH)	£20,570	8.271	£142	-0.014	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,600	8.281	£1172	-0.004	Dominated
Linagliptin-metformin -> Met-I(NPH)	£21,689	8.279	£1261	-0.006	Dominated
Metformin-sitagliptin -> Met-I(NPH)	£21,733	8.268	£1305	-0.016	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,282	8.272	£2854	-0.012	Dominated
Liraglutide-metformin -> Met-I(NPH)	£23,798	8.302	£3370	0.018	£190,731

(a) Met-I(NPH): metformin-NPH insulin

4.7.3 Assumed daily drug doses

Using the assumed daily drug doses rather than those based on included studies reduced the lifetime discounted costs for each treatment option, as metformin-NPH insulin was cheaper using assumed daily drug doses (see table 130). RCT based drug doses and assumed daily drug doses showed little variation (see table 81). Cost differences between the DPP-4 inhibitor-metformin treatment options were reduced, but metformin-pioglitazone remained the most cost-effective option at the maximum acceptable ICER of £20,00/QALY.

Table 130: First intensification sensitivity analysis – assumed daily drug doses

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,084	8.220			
Metformin-sulfonylurea -> Met-I(NPH)	£20,244	8.221	£160	0.001	Ext. dom.
Metformin-vildagliptin -> Met-I(NPH)	£21,264	8.256	£1181	0.037	£32,329
Linagliptin-metformin -> Met-I(NPH)	£21,361	8.258	£97	0.001	Ext. dom.
Metformin-sitagliptin -> Met-I(NPH)	£21,370	8.247	£105	-0.010	Dominated
Exenatide-metformin -> Met-I(NPH)	£22,917	8.259	£1653	0.003	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,179	8.289	£1915	0.033	£58,631

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom.: extendedly dominated

4.7.4 Baseline hypoglycaemia rates

When baseline hypoglycaemia rates were halved, lifetime discounted costs were slightly reduced (due to less serious hypoglycaemic episodes). Metformin-pioglitazone remained the cheapest first intensification treatment option, but metformin-sulfonylurea was no longer dominated, as the influence of hypoglycaemia was reduced (see table 131). Metformin-sulfonylurea had an ICER of £21,400/QALY compared with metformin-pioglitazone.

Table 131: First intensification sensitivity analysis – low baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,350	8.204			
Metformin-sulfonylurea -> Met-I(NPH)	£20,480	8.210	£130	0.006	£21,402
Metformin-vildagliptin -> Met-I(NPH)	£21,527	8.241	£1047	0.031	£33,805
Linagliptin-metformin -> Met-I(NPH)	£21,601	8.240	£74	0.000	Dominated
Metformin-sitagliptin -> Met-I(NPH)	£21,654	8.231	£127	-0.010	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,199	8.245	£1672	0.004	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,711	8.273	£2184	0.032	£67,734

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom.: extendedly dominated

Table 132: First intensification sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,453	8.242			
Metformin-sulfonylurea -> Met-I(NPH)	£20,608	8.224	£156	-0.018	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,630	8.274	£1177	0.032	Ext. dom.
Linagliptin-metformin -> Met-I(NPH)	£21,700	8.277	£1247	0.036	£35,072
Metformin-sitagliptin -> Met-I(NPH)	£21,751	8.267	£52	-0.010	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,306	8.279	£1607	0.001	Ext. dom.
Liraglutide-metformin -> Met-I(NPH)	£23,820	8.307	£2120	0.030	£71,135

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom: extendedly dominated

Similarly, when baseline hypoglycaemia rates were doubled, the influence of hypoglycaemia increased (see table 132). In both sensitivity analyses, metformin-vildagliptin was the DPP-4

inhibitor-metformin treatment option with the lowest ICER, but QALY differences between DPP-4 inhibitor-metformin treatment options were small.

4.7.5 Treatment effect adjustment for baseline HbA1c

When the original health economic model was run without the treatment effect adjustment for baseline HbA1c, the first intensification incremental results were very similar to the base case results (see table 133).

Table 133: First intensification sensitivity analysis – no treatment effect adjustment for baseline HbA1c

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,049	8.233			
Metformin-sulfonylurea -> Met-I(NPH)	£20,186	8.233	£136	0.000	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,313	8.271	£1264	0.038	£33,280
Linagliptin-metformin -> Met-I(NPH)	£21,388	8.273	£75	0.002	£34,406
Metformin-sitagliptin -> Met-I(NPH)	£21,410	8.265	£22	-0.009	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,165	8.279	£1777	0.006	Ext.dom.
Liraglutide-metformin -> Met-I(NPH)	£23,663	8.304	£2274	0.031	£73,747

(a) Met-I(NPH): metformin-NPH insulin
(b) Ext. dom: extendedly dominated

4.8 First intensification – discussion and conclusions

In all analyses, metformin-pioglitazone was the cheapest first intensification treatment option. This was due to low treatment costs and hypoglycaemia costs. Unless baseline hypoglycaemia rates were low, metformin-sulfonylurea was dominated by metformin-pioglitazone. The lifetime discounted cost (£132) and QALY (-0.004) differences between metformin-pioglitazone and metformin-sulfonylurea were small but were sustained in 1000 PSA iterations.

The differences – particularly lifetime discounted cost differences – between the DPP-4 inhibitor-metformin treatment options (linagliptin, sitagliptin and vildagliptin) were small and the GDG were happy to consider these treatment options to be similar enough to each other. Linagliptin-metformin had the lowest ICER (£36,800/QALY) compared with metformin-pioglitazone. In sensitivity analyses, the ICERs for the cheapest DPP-4 inhibitor treatment option compared with metformin-pioglitazone or metformin-sulfonylurea remained between £32,000/QALY and dominated. The only sensitivity analysis where a DPP-4 inhibitor-metformin treatment option did not have an ICER between £32,000/QALY and £38,000/QALY compared with metformin-pioglitazone was when treatment-related weight gain only lasted 1 year (all DPP-4 inhibitor-metformin options were dominated by metformin-pioglitazone). This highlighted the sensitivity of the analysis to the weight profile assumptions made.

Given the known contraindiciations for prescribing pioglitazone, the GDG assessed the decision space without metformin-pioglitazone. Metformin-sulfonylurea was the cheapest treatment option remaining; metformin-vildagliptin had an ICER of £29,300/QALY compared with metformin-sulfonylurea.

In all analyses, GLP-1 agonist-metformin treatment options were not cost effective compared with DPP-4 inhibitor-metformin treatment options. Exenatide-metformin was dominated or extendedly dominated; liraglutide-metformin had an ICER well in excess of the maximum

accepted ICER of £20,000/QALY. The existing guideline (National Institute for Health and Care Excellence 2009) included stopping rules for GLP-1 agonists that were not able to be incorporated into the original health economic model.

Due to a lack of clinical data, it was not possible to include any meglitinide-containing treatment options in the base case of the original health economic model. The year-2 data sensitivity analyses indicated metformin-nateglinide was not dissimilar to DPP-4 inhibitor-metformin treatment options, but was extendedly dominated by them. Given the cost effectiveness of repaglinide at initial therapy for people who could not take metformin, it would have been beneficial to be able to model first intensification treatment options that included repaglinide. However, repaglinide is only licensed in combination with metformin and the minimum dataset was not available for metformin-repaglinide.

Due to a lack of clinical data, it was not possible to include any non-metformin-based treatment options in the base case of the original health economic model. The year-2 data sensitivity analyses indicated that pioglitazone-sulfonylurea was a poor option compared with metformin-based treatment options, primarily due to large lifetime discounted QALY losses from treatment-related weight-gain. However, a more appropriate comparison for pioglitazone-sulfonylurea would have been to other non-metformin based options such as pioglitazone-sitagliptin or sitagliptin-sulfonylurea but this was not possible.

Differences between treatment options at first intensification were small, due to the normalising effect of future intensifications in the economic model – people were only on their first intensification therapies for an average of 3.7 years. Lifetime discounted QALY differences between the most effective (liraglutide-metformin) and least effective (metformin-sulfonylurea) treatments in the base case were small – less than 26 quality-adjusted life-days out of 8.2 remaining QALYs. Cost differences were largely due to the costs of the drugs themselves.

Whilst sensitivity analyses indicated the cost-effectiveness results were partially sensitive to model structure and parameters related to treatment-related weight-change and hypoglycaemia, the conclusions drawn remained fairly robust. Like for initial therapy, the choice of weight profile had the largest influence, with the baseline hypoglycaemia rate also influencing cost-effectiveness results.

4.9 Second intensification – base-case results

When averaged across all 20 modelled therapies, the simulated cohort starting on second intensification therapy survived for an average of 13.9 undiscounted life years – given an average starting age of 65.4, people survived until an average age of 79.3 years. Survival was primarily a function of HbA1c treatment effect (see table 58) and survival on different treatment options varied by less than 90 days with 3 oral drug treatment options producing lower survival and some biphasic insulin treatment options producing higher survival (see table 134)

Table 134: Life years gained In original health economic model for second intensification treatment options

Treatment	Life years
Metformin-sitagliptin-sulfonylurea	13.792
Metformin-pioglitazone-sulfonylurea	13.812
Metformin-NPH insulin-sulfonylurea	13.846
NPH insulin-sulfonylurea	13.902
Insulin glargine-sulfonylurea	13.914
Insulin detemir-metformin	13.925
Insulin degludec-metformin	13.929
NPH insulin	13.940
Insulin glargine-metformin	13.942
Insulin degludec/aspart mix-metformin	13.952
Exenatide-metformin-sulfonylurea	13.955
Biphasic insulin aspart-metformin-sulfonylurea	13.960
Insulin glargine-metformin-sulfonylurea	13.964
Insulin lispro mix 50 and mix 25	13.965
Metformin-NPH insulin	13.968
Insulin lispro mix 50/50-metformin	13.970
Biphasic insulin aspart-repaglinide	13.975
Liraglutide-metformin-sulfonylurea	13.983
Biphasic insulin aspart-metformin	13.992
Metformin-NPH insulin-repaglinide	14.034

4.9.1 Clinical outcomes

Compared with initial therapy and first intensification, there were slightly greater differences in the mean lifetime event rates for UKPDS complications (see table 135). This was due to a lack of further intensifications to the same treatment and some slightly greater differences in HbA1c treatment effect.

4.9.2 Lifetime discounted QALYs

People who started the original health economic model at second intensification gained between 6.5 and 7.0 lifetime discounted QALYs (see table 136). QALY losses associated with treatment-related weight-changes ranged from 0.3 to 0.5 lifetime discounted QALYs and from symptomatic hypoglycaemia they ranged from 0.2 to 0.6 lifetime discounted QALYs.

Treatment options that gained the most lifetime discounted QALYs included GLP-1 agonists (exenatide and liraglutide) in combination with metformin and sulfonylurea and longer-acting insulins (detemir, degludec, glargine and NPH) in combination with metformin.

Table 135: Mean lifetime event rates for second intensification of therapy

Treatment	Amputation	Blindness	Renal failure	CHF	IHD	MI	Stroke	Life Years
Metformin-Sitagliptin-Sulfonylurea	0.04324	0.06662	0.02721	0.14350	0.10338	0.31981	0.13806	13.792
Metformin-Pioglitazone-Sulfonylurea	0.04248	0.06586	0.02720	0.14269	0.10293	0.31804	0.13738	13.812
Metformin-NPH insulin-Sulfonylurea	0.04131	0.06467	0.02712	0.14116	0.10219	0.31553	0.13598	13.846
NPH insulin-Sulfonylurea	0.03969	0.06295	0.02713	0.13921	0.10109	0.31171	0.13429	13.902
Insulin Glargine-Sulfonylurea	0.03785	0.06086	0.02706	0.13650	0.09952	0.30673	0.13190	13.914
Insulin Detemir-Metformin	0.03887	0.06204	0.02708	0.13793	0.10037	0.30946	0.13324	13.925
Insulin Degludec-Metformin	0.03824	0.06130	0.02707	0.13701	0.09996	0.30791	0.13247	13.929
NPH insulin	0.03851	0.06163	0.02708	0.13747	0.10018	0.30874	0.13292	13.940
Insulin Glargine-Metformin	0.03910	0.06230	0.02712	0.13821	0.10056	0.30996	0.13352	13.942
Insulin degludec/aspart mix-Metformin	0.03818	0.06121	0.02705	0.13689	0.09978	0.30753	0.13232	13.952
Exenatide-Metformin-Sulfonylurea	0.03766	0.06053	0.02706	0.13613	0.09937	0.30595	0.13166	13.955
Biphasic Insulin Aspart-Metformin-Sulfonylurea	0.03713	0.06003	0.02703	0.13531	0.09889	0.30444	0.13091	13.960
Insulin Glargine-Metformin-Sulfonylurea	0.03849	0.06166	0.02711	0.13753	0.10015	0.30864	0.13279	13.964
Insulin lispro mix 50 and mix 25	0.03932	0.06252	0.02707	0.13858	0.10062	0.31059	0.13378	13.965
Metformin-NPH insulin	0.03740	0.06028	0.02707	0.13563	0.09911	0.30508	0.13116	13.968
Insulin lispro mix 50/50-Metformin	0.03786	0.06081	0.02709	0.13648	0.09956	0.30664	0.13200	13.970
Biphasic Insulin Aspart-Repaglinide	0.03799	0.06099	0.02705	0.13670	0.09964	0.30706	0.13212	13.975
Liraglutide-Metformin-Sulfonylurea	0.03770	0.06073	0.02707	0.13619	0.09942	0.30628	0.13177	13.983
Biphasic Insulin Aspart-Metformin	0.03777	0.06077	0.02702	0.13635	0.09947	0.30643	0.13187	13.992
Metformin-NPH insulin-Repaglinide	0.03581	0.05823	0.02704	0.13290	0.09752	0.29986	0.12881	14.034

(a) Results shown are from a single base case model run of 50,000 people through 1000 loops
(b) Event rates and life years are undiscounted
(c) CHF: congestive heart failure; IHD: ischaemic heart disease; MI: myocardial infarction
(d) For definitions of events, see Appendix F.2 of this document

Table 136: Mean lifetime discounted QALYs for second intensification of therapy

Treatment	UKPDS	Hypoglycaemia		Weight	Treatment switches	Total
		Symptomatic	Severe			
Insulin lispro mix 50 and mix 25	7.891	-0.603	-0.139	-0.330	0.000	6.819
Biphasic insulin aspart-repaglinide	7.898	-0.408	-0.049	-0.452	-0.003	6.986
Metformin-NPH insulin-sulfonylurea	7.810	-0.413	-0.048	-0.327	0.000	7.021
Biphasic insulin aspart-metformin	7.909	-0.445	-0.055	-0.384	-0.001	7.024
Biphasic insulin aspart-metformin-sulfonylurea	7.888	-0.423	-0.049	-0.356	0.000	7.060
NPH insulin	7.874	-0.420	-0.048	-0.343	0.000	7.063
NPH insulin-sulfonylurea	7.849	-0.384	-0.039	-0.325	0.000	7.101
Insulin lispro mix 50/50-metformin	7.894	-0.401	-0.048	-0.322	-0.002	7.121
Insulin degludec/aspart mix-metformin	7.882	-0.410	-0.050	-0.289	-0.002	7.131
Metformin-sitagliptin-sulfonylurea	7.774	-0.303	-0.031	-0.307	0.000	7.133
Insulin glargine-sulfonylurea	7.857	-0.348	-0.031	-0.340	0.000	7.137
Metformin-pioglitazone-sulfonylurea	7.788	-0.277	-0.023	-0.341	0.000	7.147
Metformin-NPH insulin-repaglinide	7.938	-0.393	-0.048	-0.335	-0.002	7.160
Insulin glargine-metformin-sulfonylurea	7.891	-0.350	-0.031	-0.334	0.000	7.176
Metformin-NPH insulin	7.894	-0.343	-0.030	-0.289	0.000	7.231
Exenatide-metformin-sulfonylurea	7.884	-0.353	-0.032	-0.265	-0.001	7.233
Insulin glargine-metformin	7.876	-0.305	-0.025	-0.279	-0.001	7.266
Insulin detemir-metformin	7.864	-0.271	-0.021	-0.261	-0.001	7.310
Insulin degludec-metformin	7.867	-0.237	-0.018	-0.288	-0.001	7.323
Liraglutide-metformin-sulfonylurea	7.903	-0.259	-0.019	-0.271	0.000	7.354

(a) UKPDS: QALYs gained within UKPDS OM1 as a result of survival and long term complications

Table 137: Mean lifetime discounted costs for second intensification of therapy

Treatment	UKPDS	Treatment Costs	Severe Hypoglycaemia	Treatment switches	Total
Metformin-pioglitazone-sulfonylurea	£14,838	£1744	£775	£3	£17,360
NPH insulin-sulfonylurea	£14,757	£5408	£1308	£2	£21,476
Metformin-NPH insulin-sulfonylurea	£14,806	£5342	£1639	£2	£21,789
Metformin-sitagliptin-sulfonylurea	£14,855	£5931	£1088	£3	£21,877
Insulin glargine-metformin-sulfonylurea	£14,709	£6368	£1053	£0	£22,130
Metformin-NPH insulin	£14,703	£6588	£998	£4	£22,293
Insulin degludec/aspart mix-metformin	£14,711	£6071	£1730	£18	£22,531
Biphasic insulin aspart-repaglinide	£14,698	£6253	£1656	£32	£22,639
Metformin-NPH insulin-repaglinide	£14,649	£6574	£1639	£16	£22,879
Insulin glargine-sulfonylurea	£14,753	£7082	£1056	£2	£22,893
Biphasic insulin aspart-metformin-sulfonylurea	£14,712	£6538	£1675	£1	£22,926
NPH insulin	£14,726	£6811	£1616	£1	£23,154
Insulin glargine-metformin	£14,721	£8190	£835	£6	£23,752
Biphasic insulin aspart-metformin	£14,684	£7527	£1870	£8	£24,089
Insulin detemir-metformin	£14,740	£8916	£704	£10	£24,370
Insulin lispro mix 50/50-metformin	£14,699	£8221	£1615	£21	£24,556
Exenatide-metformin-sulfonylurea	£14,716	£10,008	£1084	£9	£25,818
Insulin degludec-metformin	£14,736	£10,482	£611	£5	£25,835
Insulin lispro mix 50 and mix 25	£14,708	£6903	£4696	£0	£26,307
Liraglutide-metformin-sulfonylurea	£14,688	£16,141	£635	£1	£31,465

(a) UKPDS: costs gained within UKPDS OM1 as a result of survival and long term complications

4.9.3 Lifetime discounted costs

The biggest proportion of lifetime discounted costs (between 47% and 85%) were incurred as a result of UKPDS OM1-modelled complications (see table 138). The costs of the modelled pharmacological treatments themselves accounted for most variation in lifetime discounted costs and there was also variation in the costs for severe hypoglycaemia.

Metformin-pioglitazone-sulfonylurea had the lowest lifetime discounted costs; liraglutide-metformin-sulfonylurea had the highest lifetime discounted costs (driven by a high liraglutide dose, see table 68).

4.9.4 Incremental cost–utility results

Metformin-pioglitazone-sulfonylurea had the lowest lifetime discounted costs (see table 138). All other treatments were dominated or extendedly dominated, except for insulin detemir-metformin (ICER of £40,800/QALY compared with metformin-pioglitazone-sulfonylurea), and liraglutide-metformin-sulfonylurea (ICER of £172,900 per QALY compared with insulin detemir-metformin).

The cost–utility plane for second intensification (see figure 30) illustrates the lifetime discounted costs differences between treatments. As it was a combination of generic oral drugs, metformin-pioglitazone-sulfonylurea had substantially lower lifetime discounted costs than any other treatments; liraglutide-metformin-sulfonylurea had substantially higher lifetime discounted costs.

Table 138: Mean lifetime incremental cost–utility results for second intensification

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£17,279	7.147			
NPH insulin-sulfonylurea	£21,636	7.097	£4358	-0.050	Dominated
Metformin-sitagliptin-sulfonylurea	£21,763	7.126	£4484	-0.021	Dominated
Metformin-NPH insulin-sulfonylurea	£22,000	7.020	£4721	-0.127	Dominated
Metformin-NPH insulin	£22,108	7.230	£4829	0.083	Ext. dom.
Biphasic insulin aspart-repaglinide	£22,738	6.979	£5460	-0.168	Dominated
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£5591	0.026	Dominated
NPH insulin	£22,896	7.060	£5617	-0.086	Dominated
Metformin-NPH insulin-repaglinide	£22,899	7.161	£5620	0.015	Dominated
Insulin glargine-sulfonylurea	£23,260	7.135	£5982	-0.011	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£5984	-0.013	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£6025	-0.096	Dominated
Insulin glargine-metformin	£23,716	7.270	£6437	0.123	Ext. dom.
Biphasic insulin aspart-metformin	£24,028	7.013	£6750	-0.134	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£6858	-0.021	Dominated
Insulin detemir-metformin	£24,228	7.317	£6950	0.170	£40,778
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£172,890

(a) Ext. Dom: extendedly dominated

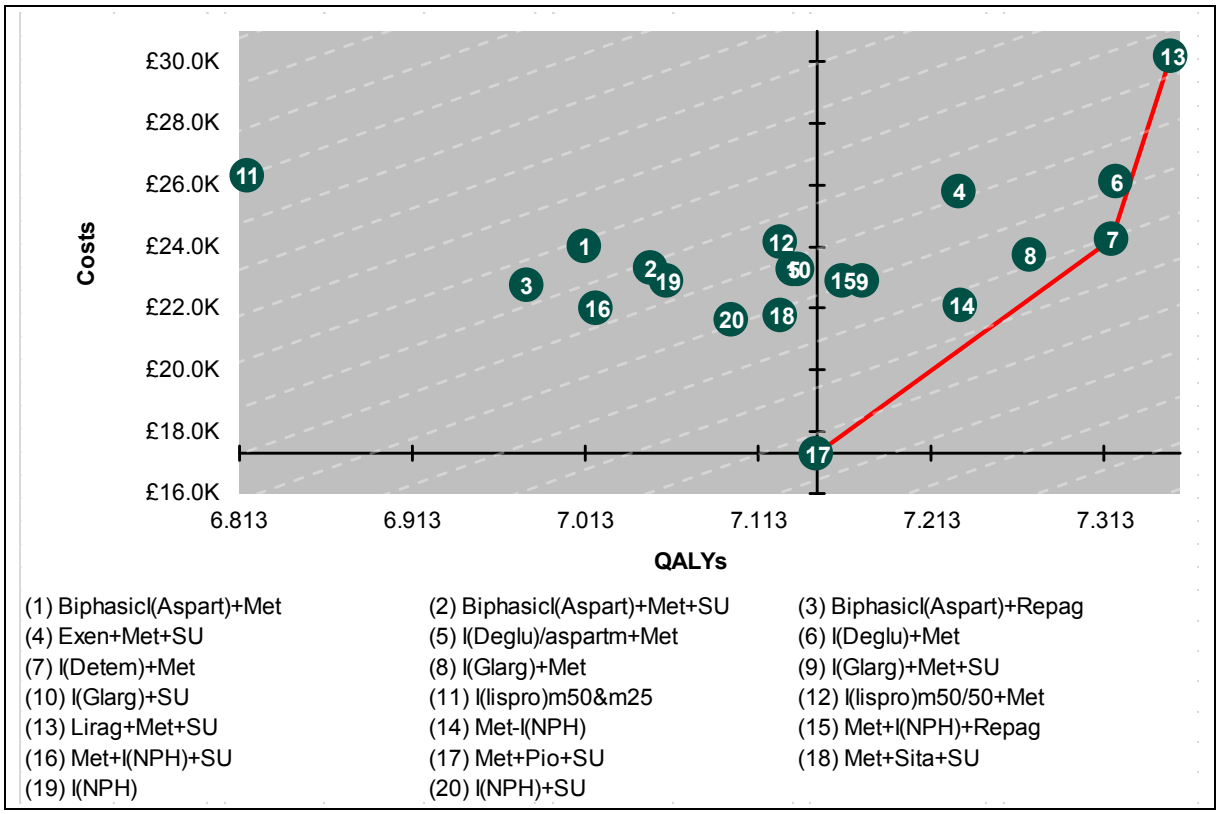


Figure 30: Cost–utility plane of mean lifetime results for second intensification

Assuming a maximum acceptable ICER of £20,000/QALY, metformin-pioglitazone-sulfonylurea was the most cost-effective second intensification treatment; this was driven by its very low lifetime discounted costs. The analysis arrived at this result despite that fact that metformin-pioglitazone-sulfonylurea had the second-worst 1-year HbA1c treatment effect – an increase of 1.3%. The GDG acknowledged the low cost of this option and considered it realistic; however, the group felt pioglitzone would be contraindicated for a large number of people with type 2 diabetes.

Accordingly, the GDG was keen to consider the second intensification decision space without the metformin-pioglitazone-sulfonylurea treatment option (see table 139). In this analysis, NPH insulin-sulfonylurea had the lowest lifetime discounted costs. Compared with NPH insulin-sulfonylurea, metformin-NPH insulin had an ICER of £3600/QALY; in turn, insulin detemir-metformin had an ICER of £24,300/QALY compared with metformin-NPH insulin. Liraglutide-metformin-sulfonylurea retained an ICER of £172,900/QALY compared with insulin degludec-metformin (see figure 31).

A number of treatment options were subject to extended dominance, but the GDG felt they remained potentially useful treatment options. In particular, the remaining 3 oral treatment option of metformin-sitagliptin-sulfonylurea was extendedly dominated by NPH insulin-sulfonylurea and metformin-NPH insulin. However, it was very close to the cost-effectiveness frontier, with expected net benefits that lie between the cheapest available option and the most cost-effective. It is of note that the minimum dataset for 3 oral treatment options containing other DPP-4 inhibitors with metformin and sulfonylurea was not available to be included in the original health economic model.

Table 139: Mean lifetime incremental cost–utility results for second intensification – when metformin-pioglitazone-sulfonylurea was not within the decision space

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
NPH insulin-sulfonylurea	£21,636	7.097			
Metformin-sitagliptin-sulfonylurea	£21,763	7.126	£127	0.029	Ext. dom.
Metformin-NPH insulin-sulfonylurea	£22,000	7.020	£364	-0.077	Dominated
Metformin-NPH insulin	£22,108	7.230	£472	0.133	£3552
Biphasic insulin aspart-repaglinide	£22,738	6.979	£631	-0.251	Dominated
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£762	-0.057	Dominated
NPH insulin	£22,896	7.060	£788	-0.169	Dominated
Metformin-NPH insulin-repaglinide	£22,899	7.161	£791	-0.068	Dominated
Insulin glargine-sulfonylurea	£23,260	7.135	£1153	-0.094	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£1155	-0.096	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£1196	-0.179	Dominated
Insulin glargine-metformin	£23,716	7.270	£1608	0.040	Ext. dom.
Biphasic insulin aspart-metformin	£24,028	7.013	£1921	-0.217	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£2028	-0.104	Dominated
Insulin detemir-metformin	£24,228	7.317	£2121	0.087	£24,260
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£172,890

(a) Ext. dom.; extendedly dominated

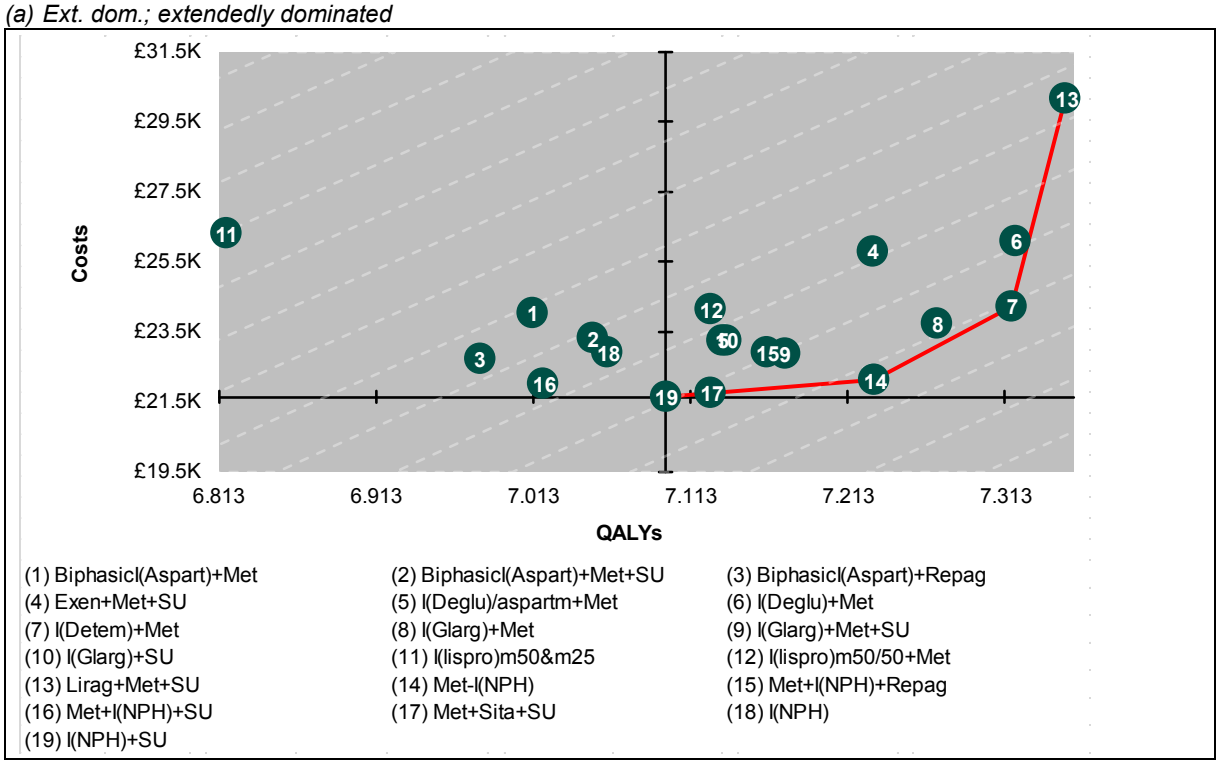


Figure 31: Cost–utility plane of mean lifetime results for second intensification – when metformin-pioglitazone-sulfonylurea was not within the decision space

The GDG expressed concern over the weight treatment effect associated with insulin detemir-metformin. The NMA for weight at 1 year was of low quality and contained 27 studies covering 25 comparators (not all of which could be included in the original health economic model). There was only 1 included study for both insulin detemir-metformin and insulin degludec-metformin; both were compared with insulin glargine-metformin. There were 5 included studies of insulin glargine-metformin and 4 included studies for metformin-NPH insulin.

In both analyses, a number of similar treatment options (longer acting insulins-metformin) clustered with comparable lifetime discounted costs and lifetime discounted QALYs – these included insulin degludec-metformin, insulin detemir-metformin, insulin glargine-metformin and metformin-NPH insulin. Exenatide-metformin-sulfonylurea was also close to this cluster of treatments.

Within this cluster of treatment options, lifetime discounted QALY differences (see table 136) were primarily driven by differences in HbA1c and weight treatment effects – treatment effects have been reproduced in table 140 for convenience. Insulin detemir-metformin had the worst HbA1c treatment effect but the best weight treatment effect.

Table 140: Absolute treatment effects - selected second intensification treatments

Treatment	HbA1c at 1yr (reduction in %)	Weight-change at 1yr (kg)	Probability of dropouts due to intolerance	Annual rate all hypoglycaemic episodes
Exenatide-metformin-sulfonylurea	-0.325	-0.121	0.126	11.863
Insulin degludec-metformin	-0.016	+1.615	0.036	5.063
Insulin detemir-metformin	+0.105	-0.390	0.099	5.669
Insulin glargine-metformin	-0.147	+1.103	0.056	7.886
Metformin-NPH Insulin	-0.535	+1.703	0.070	10.922

(a) Subset of data extracted from table 57

The primary driver of differences in lifetime discounted cost between the longer-acting insulin-metformin treatment options was treatment costs (see table 137), which in turn were driven by differing doses and unit costs (see table 141). We calculated that insulin detemir incurred a weighted average RCT dosage around 18% higher than insulin glargine, which is similar to what was assumed in the previous guideline (National Institute for Health and Care Excellence 2009).

Table 141: Ongoing daily insulin units and annual treatment costs - selected second intensification treatments

Treatment	Daily insulin units (year 2 onwards)	Annual treatment costs (Year 2 onwards)
Exenatide-metformin-sulfonylurea	2 doses exenatide	£1030
Insulin degludec-metformin	42.0	£1051
Insulin detemir-metformin	57.6	£904
Insulin glargine-metformin	48.5	£806
Metformin-NPH Insulin	57.2	£606

(a) Annual treatment costs included necessary consumable and NHS staff time
(b) Annual treatment costs All treatments included 200g/day metformin in both year 1 and year 2 onwardsfor all treatments. Exenatide-metformin-sulfonylurea also included 160mg/day metformin
(c) Subset of data extracted from table 68

Table 142: Mean lifetime incremental cost–utility results for second intensification – when 3 oral anti-diabetic agent and NPH insulin based treatment options were not within the decision space

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Biphasic insulin aspart-repaglinide	£22,738	6.979			
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£132	0.194	£678
Insulin glargine-sulfonylurea	£23,260	7.135	£391	-0.038	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£393	-0.039	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£434	-0.122	Dominated
Insulin glargine-metformin	£23,716	7.270	£846	0.097	£8,740
Biphasic insulin aspart-metformin	£24,028	7.013	£313	-0.257	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£420	-0.144	Dominated
Insulin detemir-metformin	£24,228	7.317	£513	0.047	£10,795
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£180.982

(a) Ext. dom.; extendedly dominated

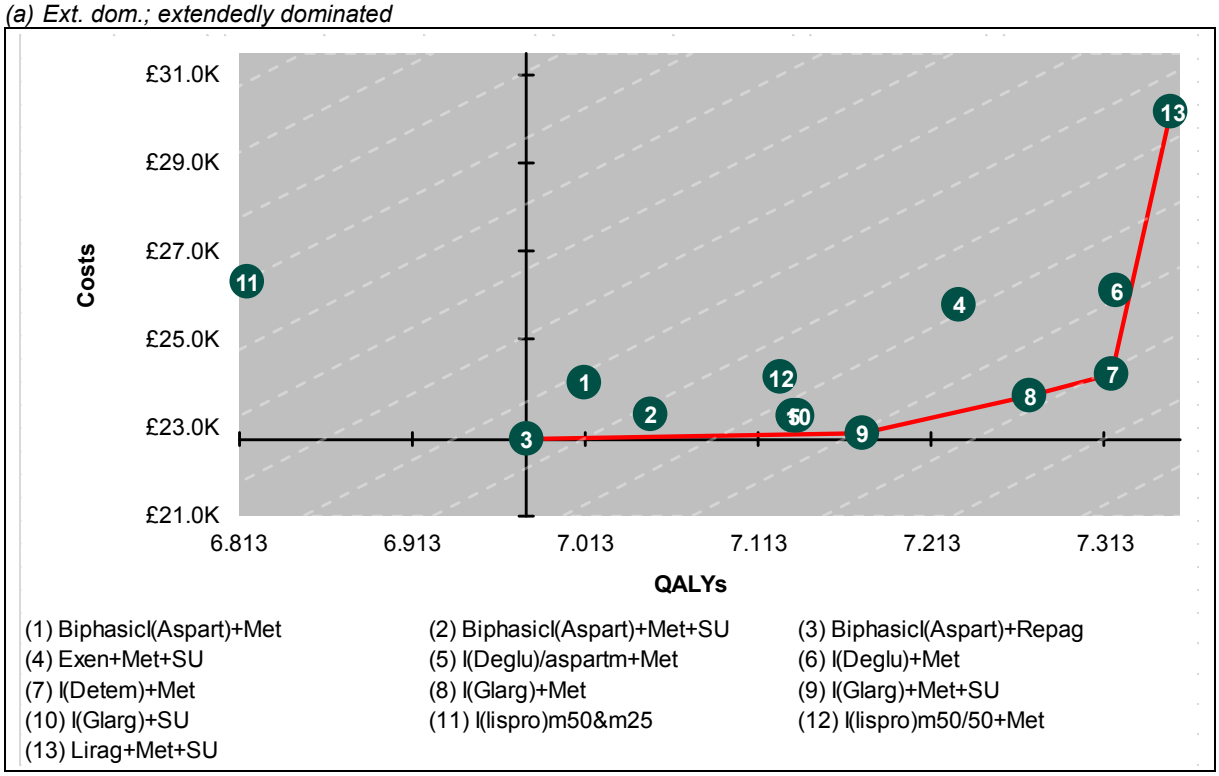


Figure 32: Cost–utility plane of mean lifetime results for second intensification – when 3 oral anti-diabetic agent and NPH insulin based treatment options were not within the decision space

The GDG were keen to consider the most cost effective treatment option for people with type diabetes who either could not tolerate 3 oral anti-diabetic or NPH insulin based treatment options or where these options failed to provide adequate HbA1c control. Whilst the analysis does not quite represent this population, the decision space without these options showed that insulin glargine-metformin had an ICER of £8700 compared with insulin glargine-metformin-sulonylurea and insulin detemir-metformin had an ICER of £10,800/QALY compared with insulin glargine-metformin (see table 142 and figure 32).

For people who could not take metformin, there were few options in the second intensification decision space. NPH insulin-sulfonylurea was the most cost-effective option for this subgroup of people (see table 143). However, the GDG were concerned they had little clinical experience with this treatment option and preferred to also recommend NPH insulin alone as a treatment option. The increased lifetime discounted costs for NPH insulin were driven by conspicuously different weighted average insulin doses – NPH insulin alone has 100 units/day whereas NPH insulin-sulfonylurea had 21 units/day (see table 68). The QALY differences between treatment options were driven more by hypoglycaemia than weight (see table 136).

Table 143: Mean lifetime incremental cost–utility results for second intensification when metformin cannot be tolerated

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
NPH insulin-sulfonylurea	£21,636	7.097			
Biphasic insulin aspart-repaglinide	£22,738	6.979	£1102	-0.118	Dominated
NPH insulin	£22,896	7.060	£1260	-0.037	Dominated
Insulin glargine-sulfonylurea	£23,260	7.135	£1624	0.038	£42,369
Insulin lispro mix 50 and mix 25	£26,307	6.818	£3046	-0.317	Dominated

4.10 Second intensification – probabilistic sensitivity analyses

At second intensification, metformin-pioglitazone-sulfonylurea was the most cost-effective treatment option at a maximum acceptable ICER of £20,000/QALY in 75% of 1000 PSA iterations (see figure 33).

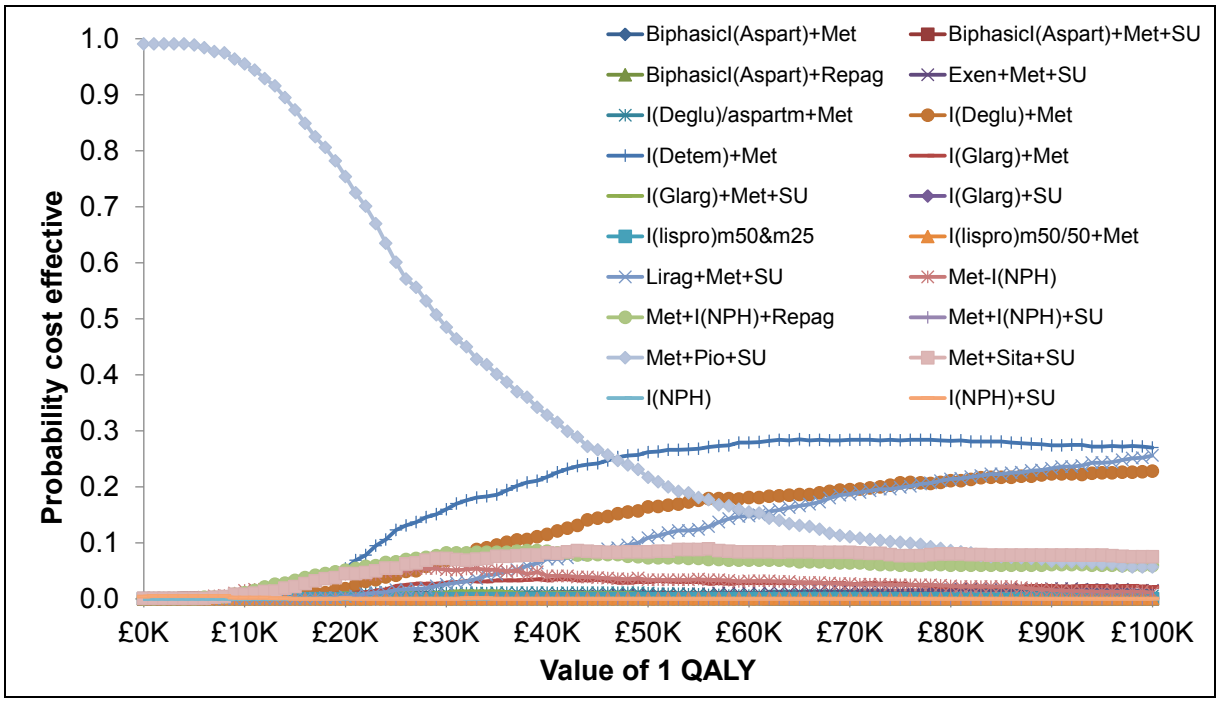


Figure 33: Cost-effectiveness acceptability curve for second intensification

When we excluded metformin-pioglitazone-sulfonylurea, there was substantial uncertainty about which of the remaining options provides best value for money. Whilst the cost-effectiveness acceptability curve (see figure 34) showed metformin-sitagliptin-sulfonylurea to

have the highest **probability** (26% of iterations) of being most cost-effective at a maximum acceptable ICER of £20,000/QALY, the cost-effectiveness acceptability frontier (see figure 35) showed metformin-NPH insulin to have the highest **expected value**. This result arises because of asymmetry in distributions of expected value (Fenwick et al. 2001) – in other words, although there were more model iterations in which metformin-sitagliptin-sulfonylurea generated greater net benefit, in the iterations where metformin-NPH insulin was superior, it was superior by a greater degree, with the net result that its average cost effectiveness is slightly greater. Insulin detemir-metformin produced greater average cost effectiveness when the willingness to pay was greater than £25,000/QALY.

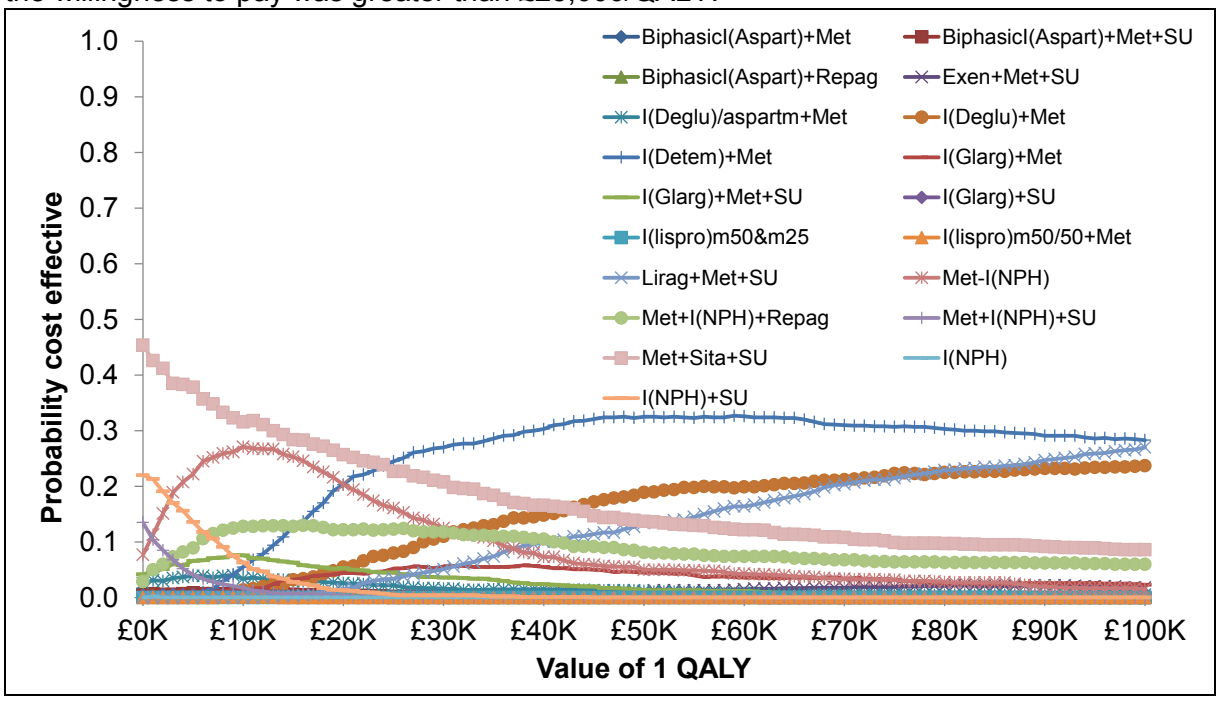


Figure 34: Cost-effectiveness acceptability curve for second intensification when metformin-pioglitazone-sulfonylurea was excluded from decision space

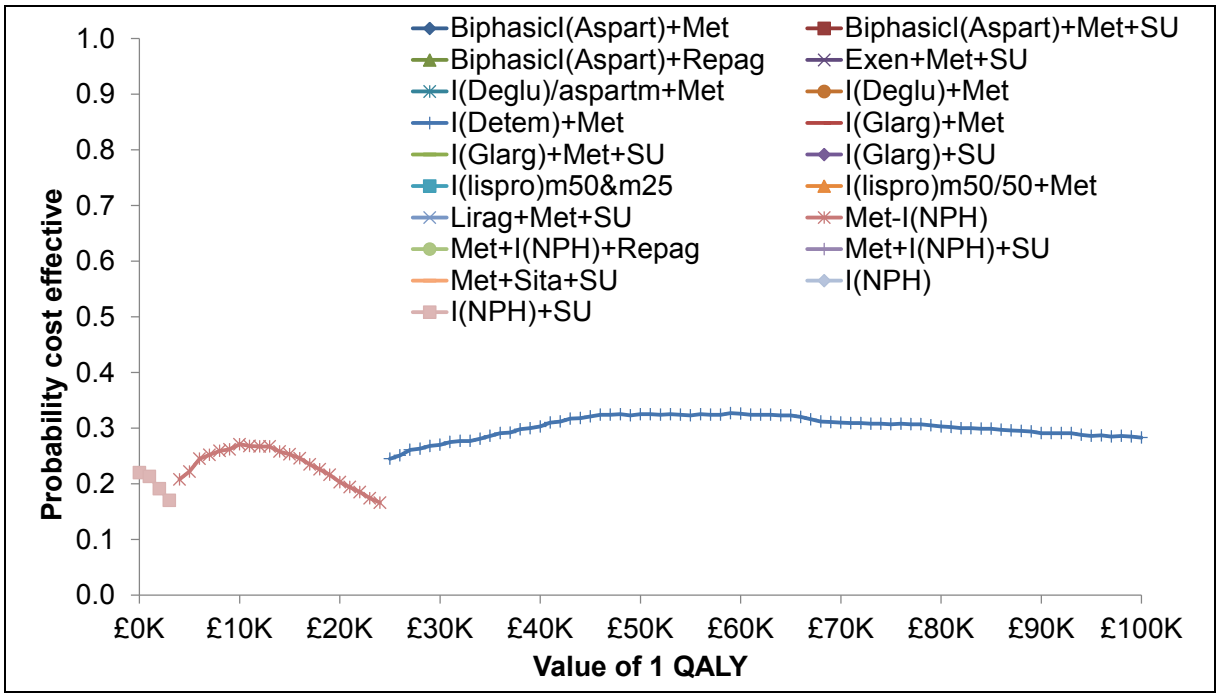
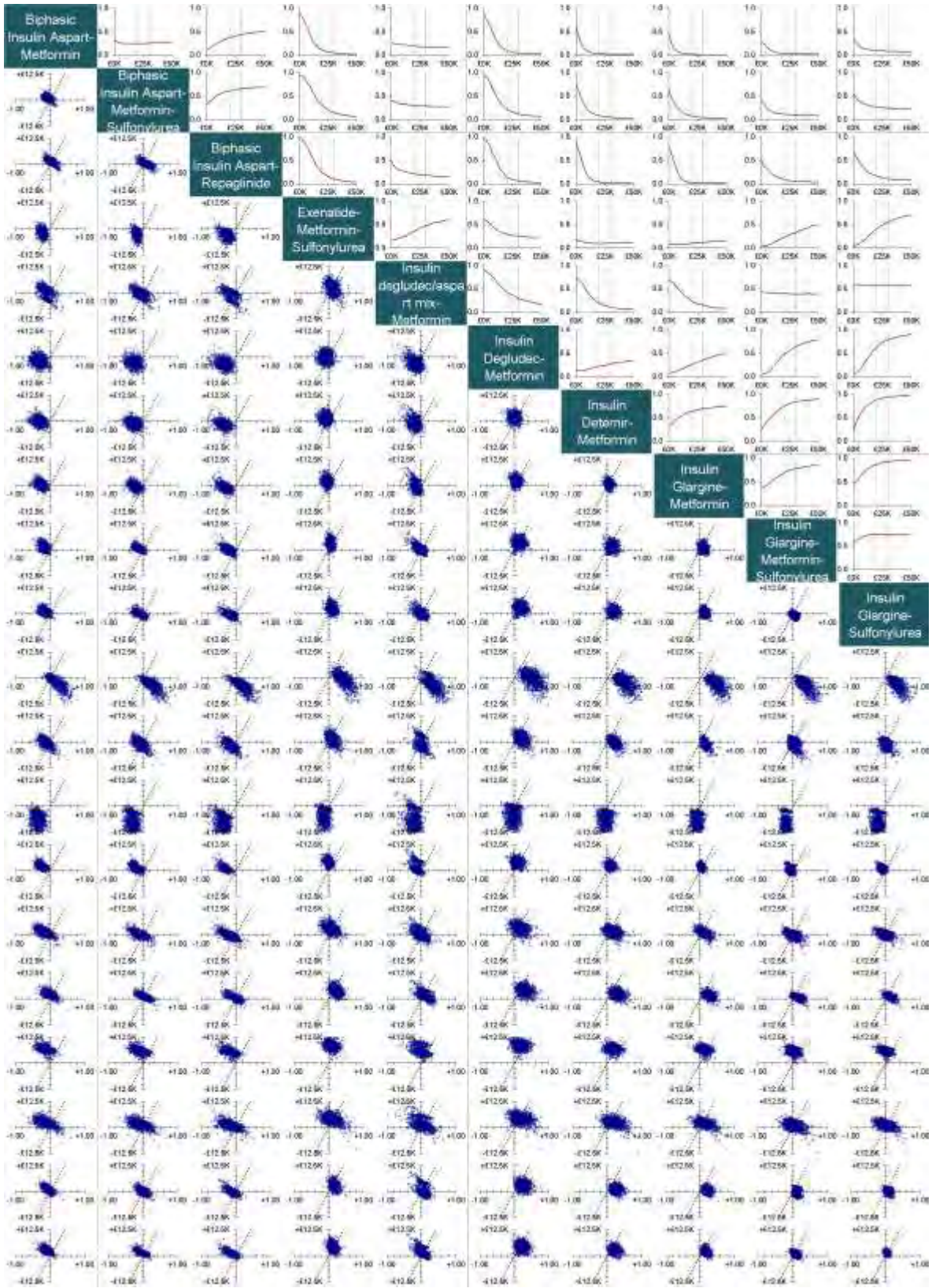


Figure 35: Cost-effectiveness acceptability frontier for second intensification when triple-oral combinations are excluded from decision space

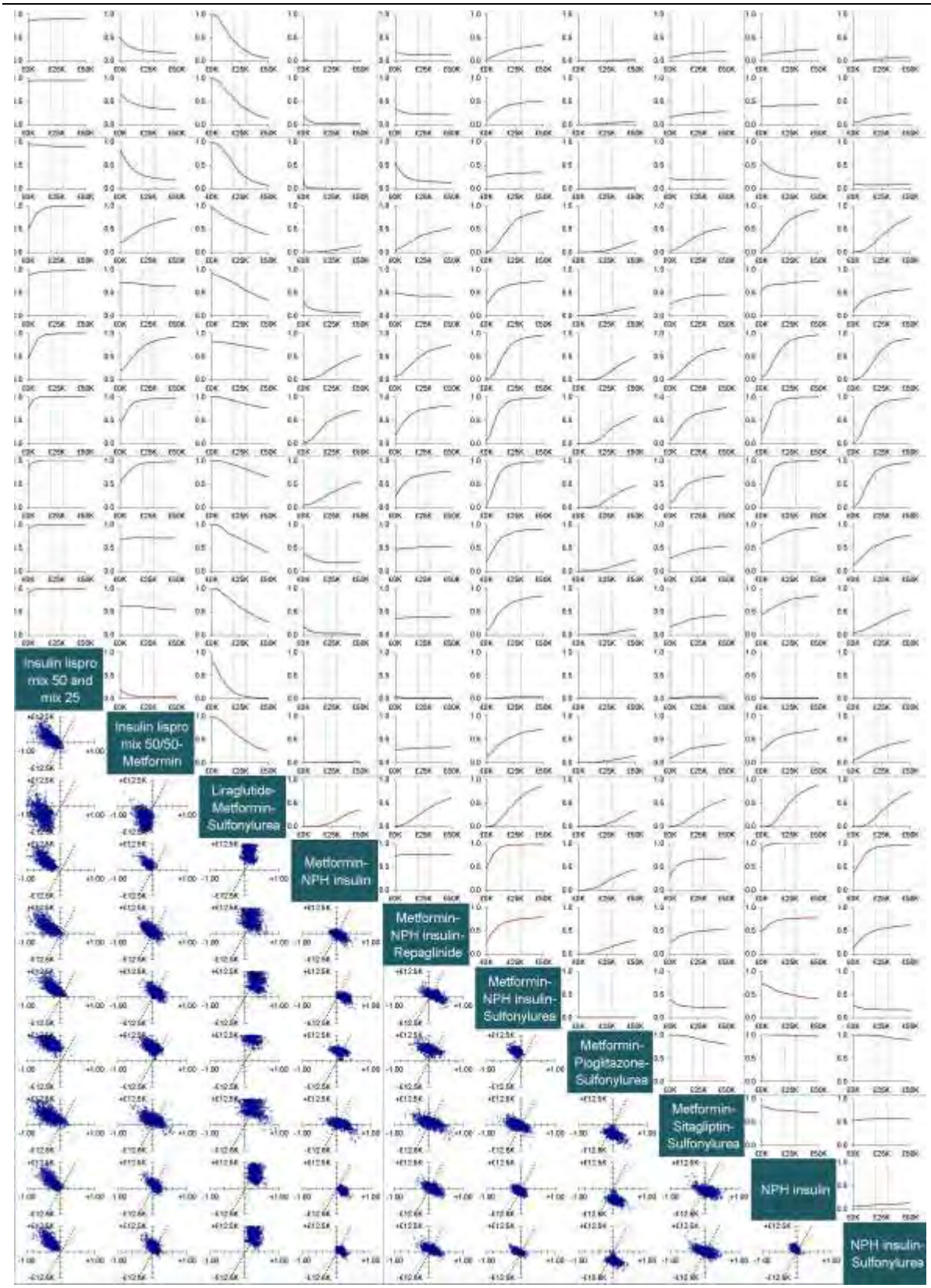
In order to further assess whether, given correlated treatment effects, there was correlation between treatment options in the PSA, pairwise treatment option were plotted, showing both the cost-effectiveness plane results scatter and the CEAC for each combination with £20,000/QALY threshold marked in green dashes and £30,000/QALY marked in red dots (see figure 36 and figure 37 – given the number of treatment options compared, it was necessary to split this figure across 2 pages).

It can be seen that, as expected from other results, the comparison between metformin-sulfonylurea-sitagliptin and metformin-NPH insulin is slightly in favour of the latter and that the comparison between metformin-NPH insulin and insulin detemir-metformin is slightly in favour of the former (unless a QALY-value threshold that is higher than conventionally accepted is adopted). It is also unsurprising to see that insulin detemir-metformin and insulin-glargine metformin are closely matched (the probability that the former provides better value, assuming a maximum acceptable ICER of £20,000/QALY, is 0.57).



Lower-left segment shows incremental costs and QALYs from each iteration of the PSA for each pairwise comparison (option above versus option to the right); upper-right segment shows cost-effectiveness acceptability curve (probability that option to the left is more cost effective than option below, at increasing values of 1 QALY).

Figure 36: Pairwise probabilistic comparisons of treatment options for second intensification of therapy (part A)



In both types of graph, a maximum acceptable ICER of £20,000/QALY is indicated by a green dashed line and a maximum acceptable ICER of £30,000/QALY is indicated by a red dotted line.

Figure 37: Pairwise probabilistic comparisons of treatment options for second intensification of therapy (part B)

4.11 Second intensification – 1-way sensitivity analyses

A number of structural assumptions inputs and were indicated for 1-way sensitivity analyses (see 3.11.2). Year-2 HbA1c and weight treatment-effect data were not available for second intensification treatment options.

4.11.1 Alternative weight profiles

As for initial therapy and first intensification, 2 sensitivity analyses were undertaken with different weight profile assumptions.

Under the assumption of a gradual weight-loss rebound, the ICERs were very similar to the base case (see table 144 and figure 38). When treatment-related weight-gain only lasts for 1 year, insulin detemir-metformin was no longer a cost-effective option (see table 145 and figure 39). Weight-gaining treatments lost fewer QALYs and the benefit to weight losing treatments was reduced.

Table 144: Second intensification sensitivity analysis – gradual weight rebound

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£16,927	7.167			
NPH insulin-sulfonylurea	£21,277	7.111	£4351	-0.057	Dominated
Metformin-sitagliptin-sulfonylurea	£21,366	7.156	£4440	-0.012	Dominated
Metformin-NPH insulin-sulfonylurea	£21,498	7.038	£4572	-0.129	Dominated
Insulin glargine-metformin-sulfonylurea	£22,060	7.187	£5133	0.020	Ext. dom.
Metformin-NPH insulin	£22,161	7.243	£5234	0.075	Ext. dom.
Insulin degludec/aspart mix-metformin	£22,200	7.140	£5274	-0.028	Dominated
Metformin-NPH insulin-repaglinide	£22,291	7.167	£5364	0.000	Dominated
Biphasic insulin aspart-repaglinide	£22,374	7.016	£5447	-0.152	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£22,729	7.069	£5803	-0.098	Dominated
Insulin glargine-sulfonylurea	£22,778	7.148	£5851	-0.019	Dominated
NPH insulin	£22,988	7.077	£6061	-0.090	Dominated
Insulin glargine-metformin	£23,801	7.290	£6874	0.122	Ext. dom.
Biphasic insulin aspart-metformin	£24,076	7.023	£7149	-0.144	Dominated
Insulin lispro mix 50/50-metformin	£24,419	7.141	£7493	-0.026	Dominated
Insulin detemir-metformin	£24,443	7.354	£7517	0.187	£40,259
Exenatide-metformin-sulfonylurea	£25,933	7.248	£1490	-0.106	Dominated
Insulin lispro mix 50 and mix 25	£25,957	6.834	£1514	-0.520	Dominated
Insulin degludec-metformin	£26,055	7.350	£1611	-0.004	Dominated
Liraglutide-metformin-sulfonylurea	£31,711	7.371	£7268	0.017	£430,836

(a) Ext. Dom: extendedly dominated

Table 145: Second intensification sensitivity analysis - weight gained is lost after 1 year

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£16,895	7.236			
NPH insulin-sulfonylurea	£21,258	7.165	£4363	-0.071	Dominated
Metformin-sitagliptin-sulfonylurea	£21,349	7.195	£4454	-0.041	Dominated
Metformin-NPH insulin-sulfonylurea	£21,471	7.096	£4576	-0.140	Dominated
Insulin glargine-metformin-sulfonylurea	£22,037	7.248	£5142	0.012	Ext. dom.
Metformin-NPH insulin	£22,139	7.264	£5244	0.028	Ext. dom.
Insulin degludec/aspart mix-metformin	£22,173	7.157	£5278	-0.079	Dominated
Metformin-NPH insulin-repaglinide	£22,258	7.223	£5363	-0.013	Dominated
Biphasic insulin aspart-repaglinide	£22,349	7.175	£5454	-0.061	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£22,707	7.151	£5812	-0.085	Dominated
Insulin glargine-sulfonylurea	£22,759	7.216	£5864	-0.020	Dominated
NPH insulin	£22,964	7.148	£6069	-0.088	Dominated
Insulin glargine-metformin	£23,776	7.300	£6881	0.064	Ext. dom.
Biphasic insulin aspart-metformin	£24,050	7.127	£7155	-0.109	Dominated
Insulin lispro mix 50/50-metformin	£24,390	7.190	£7495	-0.046	Dominated
Insulin detemir-metformin	£24,414	7.341	£7519	0.105	Ext. dom.
Exenatide-metformin-sulfonylurea	£25,921	7.241	£9026	0.005	Dominated
Insulin lispro mix 50 and mix 25	£25,936	6.894	£9041	-0.342	Dominated
Insulin degludec-metformin	£26,026	7.369	£9131	0.133	£68,815
Liraglutide-metformin-sulfonylurea	£31,675	7.371	£5649	0.002	£2,573,001

(a) Ext. Dom: extendedly dominated

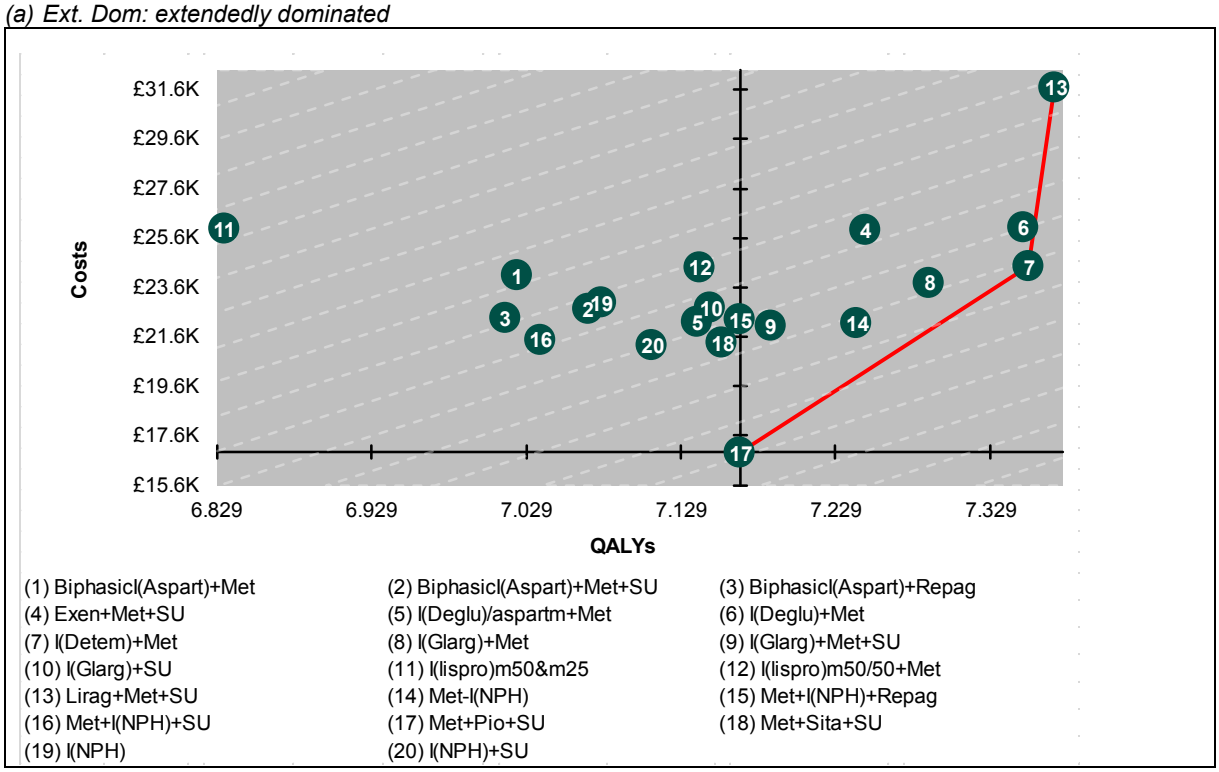


Figure 38: Cost-utility plane for second intensification gradual weight rebound sensitivity analysis

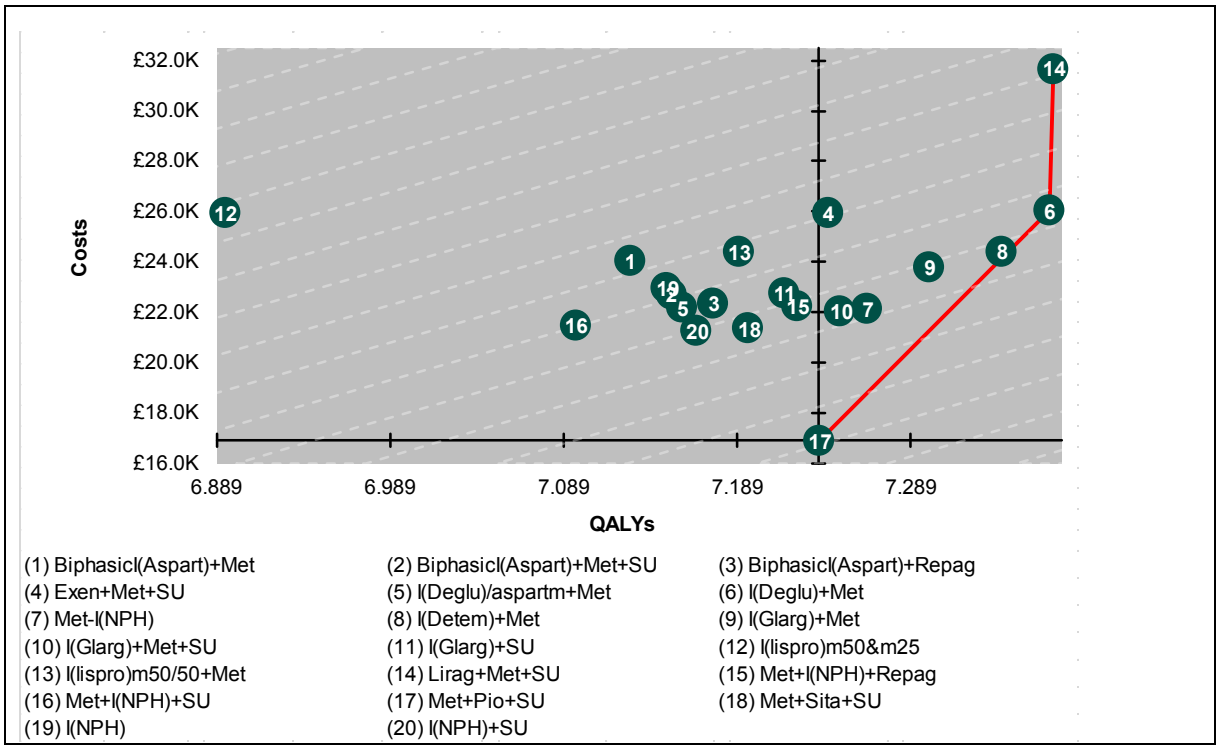


Figure 39: Cost-utility plane for second intensification weight gained is lost after 1 year sensitivity analysis

Table 146: Second intensification sensitivity analysis – gradual weight rebound when metformin-pioglitazone-sulfonylurea was not within the decision space

			Incremental		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
NPH insulin-sulfonylurea	£21,277	7.111			
Metformin-sitagliptin-sulfonylurea	£21,366	7.156	£89	0.045	£1,967
Metformin-NPH insulin-sulfonylurea	£21,498	7.038	£132	-0.118	Dominated
Insulin glargine-metformin-sulfonylurea	£22,060	7.187	£693	0.031	Ext. dom.
Metformin-NPH insulin	£22,161	7.243	£794	0.087	£9,127
Insulin degludec/aspart mix-metformin	£22,200	7.140	£39	-0.103	Dominated
Metformin-NPH insulin-repaglinide	£22,291	7.167	£130	-0.076	Dominated
Biphasic insulin aspart-repaglinide	£22,374	7.016	£213	-0.227	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£22,729	7.069	£568	-0.174	Dominated
Insulin glargine-sulfonylurea	£22,778	7.148	£617	-0.095	Dominated
NPH insulin	£22,988	7.077	£827	-0.165	Dominated
Insulin glargine-metformin	£23,801	7.290	£1640	0.047	Ext. dom.
Biphasic insulin aspart-metformin	£24,076	7.023	£1915	-0.219	Dominated
Insulin lispro mix 50/50-metformin	£24,419	7.141	£2258	-0.102	Dominated
Insulin detemir-metformin	£24,443	7.354	£2282	0.111	£20,500
Exenatide-metformin-sulfonylurea	£25,933	7.248	£1490	-0.106	Dominated
Insulin lispro mix 50 and mix 25	£25,957	6.834	£1514	-0.520	Dominated
Insulin degludec-metformin	£26,055	7.350	£1611	-0.004	Dominated
Liraglutide-metformin-sulfonylurea	£31,711	7.371	£7268	0.017	£430,836

(a) Ext. Dom: extendedly dominated

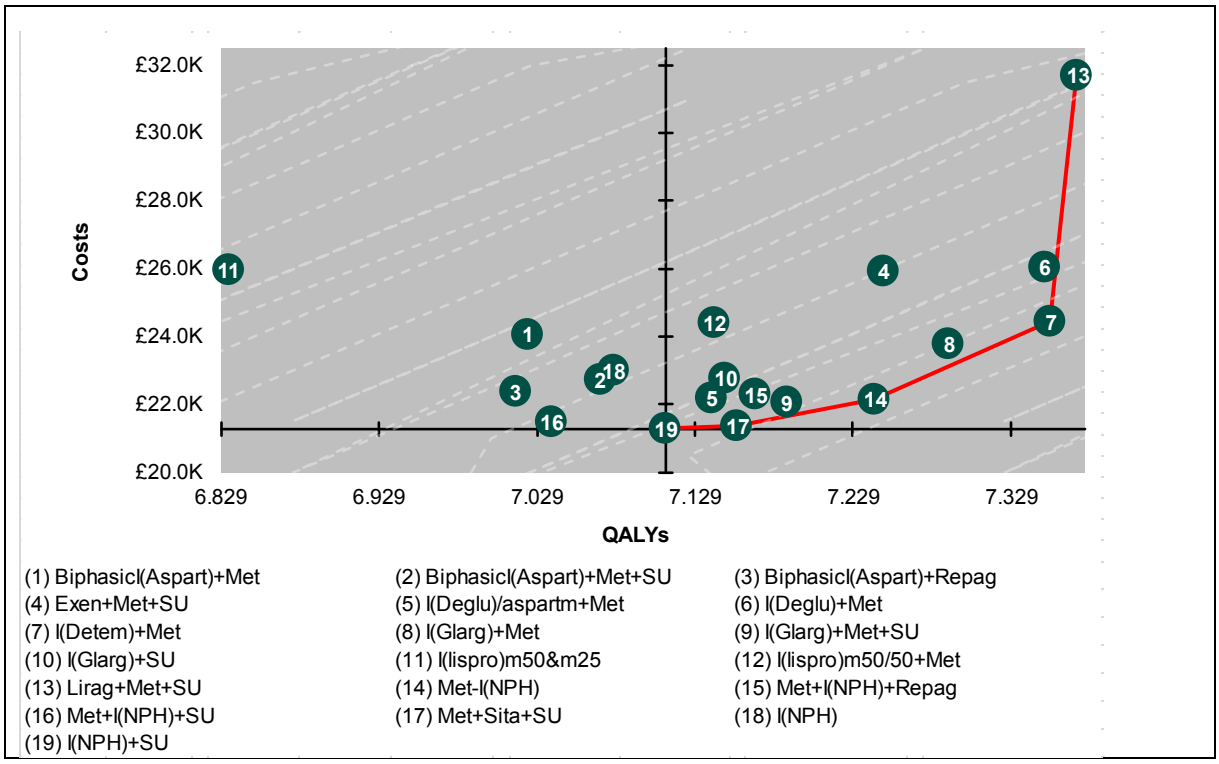


Figure 40: Cost-utility plane for second intensification gradual weight rebound sensitivity analysis when metformin-pioglitazone-sulfonylurea was not within the decision space

However, if the more gradual treatment-related weight-loss rebound scenario was considered for the decision space without metformin-pioglitazone-sulfonylurea, compared with NPH insulin-sulfonylurea, metformin-sitagliptin-sulfonylurea had an ICER of £2000/QALY, metformin-NPH insulin had an ICER of £9100/QALY compared with metformin-sitagliptin-sulfonylurea and insulin detemir-metformin had an ICER of £20,500/QALY compared with metformin-NPH insulin (see table 146 and figure 40).

If weight-gain only lasted for 1 year, compared with NPH insulin-sulfonylurea, metformin-sitagliptin-sulfonylurea had an ICER of £3000/QALY, metformin-NPH insulin had an ICER of £11,500/QALY compared with metformin-sitagliptin-sulfonylurea and insulin detemir-metformin had an ICER of £29,400/QALY compared with metformin-NPH insulin (see table 147 and figure 41).

Table 147: Second intensification sensitivity analysis - weight gained is lost after 1 year when metformin-pioglitazone-sulfonylurea was not within the decision space

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
NPH insulin-sulfonylurea	£21,258	7.165			
Metformin-sitagliptin-sulfonylurea	£21,349	7.195	£91	0.030	£3,041
Metformin-NPH insulin-sulfonylurea	£21,471	7.096	£123	-0.100	Dominated
Insulin glargine-metformin-sulfonylurea	£22,037	7.248	£688	0.053	Ext. dom.
Metformin-NPH insulin	£22,139	7.264	£790	0.069	£11,513
Insulin degludec/aspart mix-metformin	£22,173	7.157	£34	-0.107	Dominated
Metformin-NPH insulin-repaglinide	£22,258	7.223	£119	-0.041	Dominated
Biphasic insulin aspart-repaglinide	£22,349	7.175	£210	-0.089	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£22,707	7.151	£569	-0.113	Dominated
Insulin glargine-sulfonylurea	£22,759	7.216	£620	-0.048	Dominated
NPH insulin	£22,964	7.148	£825	-0.116	Dominated
Insulin glargine-metformin	£23,776	7.300	£1637	0.036	Ext. dom.
Biphasic insulin aspart-metformin	£24,050	7.127	£1911	-0.137	Dominated
Insulin lispro mix 50/50-metformin	£24,390	7.190	£2251	-0.074	Dominated
Insulin detemir-metformin	£24,414	7.341	£2275	0.077	£29,389
Exenatide-metformin-sulfonylurea	£25,921	7.241	£1507	-0.100	Dominated
Insulin lispro mix 50 and mix 25	£25,936	6.894	£1522	-0.448	Dominated
Insulin degludec-metformin	£26,026	7.369	£1612	0.027	£59,175
Liraglutide-metformin-sulfonylurea	£31,675	7.371	£5649	0.002	£2,573,001

(a) Ext. Dom: extendedly dominated

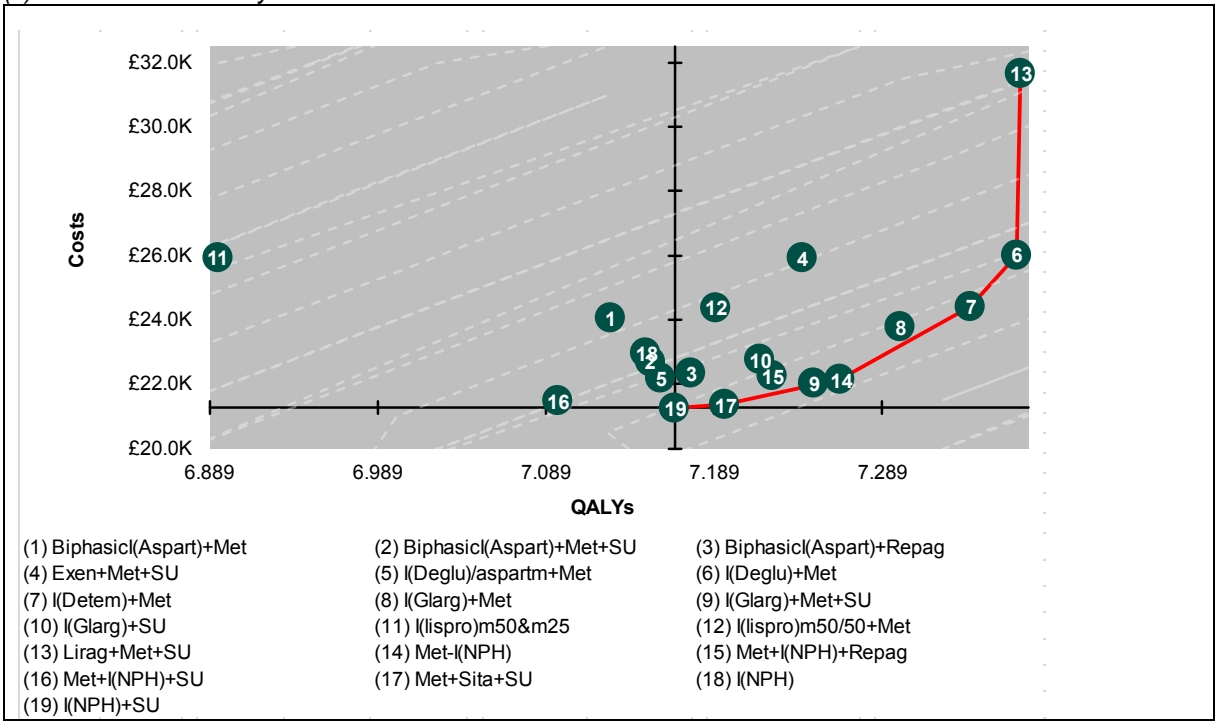


Figure 41: Cost-utility plane for second intensification weight gained is lost after 1 year sensitivity analysis when metformin-pioglitazone-sulfonylurea was not within the decision space

4.11.2 Assumed daily drug doses

Using the assumed daily drug doses rather than those based on included studies had a larger impact for second intensification than for other review sub-questions. The second intensification network nodes were often based on single RCTs so there was no weighted averaging of drug doses across RCTs.

The cost and therefore order of some treatment options changed (see table 148). Whilst metformin-pioglitazone-sulfonylurea remained the cheapest treatment option, insulin degludec-metformin became the most expensive option. The ICER for liraglutide-metformin-sulfonylurea was reduced (due to a substantial daily dose reduction from 1.8mg/day to 1.2mg/day) but was still substantially higher than any plausibly acceptable ICER.

Given the base case was based on substantially different NPH insulin doses for NPH insulin alone (100 units/day) and NPH insulin-sulfonylurea (21 units/day), the treatment options for people who cannot toleratue metformin were analysesd using assumed daily doses. For people who could not take metformin, NPH insulin-sulonylurea remained the cheapest and most cost-effective treatment option (see Table 149).

Table 148: Second intensification sensitivity analysis – assumed daily drug doses

			Incremental		
Treatment	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£16,626	7.145			
Metformin-sitagliptin-sulfonylurea	£20,996	7.134	£4370	-0.012	Dominated
Metformin-NPH insulin	£21,504	7.220	£4878	0.075	Ext. dom.
NPH insulin-sulfonylurea	£21,775	7.089	£5149	-0.056	Dominated
NPH insulin	£22,079	7.056	£5453	-0.089	Dominated
Biphasic insulin aspart-repaglinide	£22,274	6.994	£5648	-0.151	Dominated
Metformin-NPH insulin-sulfonylurea	£22,302	7.016	£5676	-0.129	Dominated
Metformin-NPH insulin-repaglinide	£22,682	7.146	£6056	0.000	Dominated
Insulin lispro mix 50/50-metformin	£23,162	7.119	£6536	-0.027	Dominated
Insulin glargine-metformin	£23,546	7.267	£6920	0.122	Ext. dom.
Biphasic insulin aspart-metformin	£23,648	7.003	£7022	-0.143	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,795	7.048	£7169	-0.098	Dominated
Insulin glargine-sulfonylurea	£23,966	7.127	£7340	-0.019	Dominated
Insulin detemir-metformin	£24,179	7.325	£7553	0.180	£41,914
Insulin glargine-metformin-sulfonylurea	£24,257	7.165	£79	-0.161	Dominated
Insulin degludec/aspart mix-metformin	£25,576	7.117	£1397	-0.208	Dominated
Exenatide-metformin-sulfonylurea	£25,712	7.225	£1533	-0.100	Dominated
Insulin lispro mix 50 and mix 25	£26,064	6.814	£1885	-0.511	Dominated
Liraglutide-metformin-sulfonylurea	£26,626	7.348	£2447	0.022	£109,024
Insulin degludec-metformin	£26,890	7.327	£264	-0.021	Dominated

(a) Ext. Dom: Extendedly Dominated

Table 149: Second intensification when metformin cannot be tolerated sensitivity analysis – assumed daily drug doses

Therapy	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
NPH insulin-sulfonylurea	£21,775	7.089			
NPH insulin	£22,079	7.056	£304	-0.033	Dominated
Biphasic insulin aspart-repaglinide	£22,274	6.994	£499	-0.095	Dominated
Insulin glargine-sulfonylurea	£23,966	7.127	£2191	0.037	£58,689
Insulin lispro mix 50 and mix 25	£26,064	6.814	£2098	-0.313	Dominated

4.11.3 Baseline hypoglycaemia rates

When we halved baseline hypoglycaemia rates, lifetime discounted costs reduced (due to less serious hypoglycaemic episodes) and lifetime discounted QALYs increased (due to fewer QALYs lost from less symptomatic and serious hypoglycaemic episodes). Whilst in both sensitivity analyses the incremental costs and QALYs for each treatment altered, the overall conclusions did not (see table 150 and table 151).

Table 150: Second intensification sensitivity analysis – low baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£16,482	7.274			
NPH insulin-sulfonylurea	£20,550	7.225	£4069	-0.049	Dominated
Metformin-NPH insulin-sulfonylurea	£20,647	7.154	£4165	-0.120	Dominated
Metformin-sitagliptin-sulfonylurea	£20,871	7.265	£4389	-0.009	Dominated
Insulin degludec/aspart mix-metformin	£21,316	7.257	£4834	-0.017	Dominated
Metformin-NPH insulin-repaglinide	£21,435	7.285	£4953	0.011	Ext. dom.
Insulin glargine-metformin-sulfonylurea	£21,449	7.301	£4967	0.027	Ext. dom.
Metformin-NPH insulin	£21,570	7.356	£5088	0.082	Ext. dom.
Biphasic insulin aspart-repaglinide	£21,578	7.133	£5097	-0.141	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£21,841	7.187	£5359	-0.087	Dominated
NPH insulin	£22,138	7.195	£5657	-0.079	Dominated
Insulin glargine-sulfonylurea	£22,162	7.261	£5681	-0.013	Dominated
Biphasic insulin aspart-metformin	£23,030	7.146	£6548	-0.128	Dominated
Insulin glargine-metformin	£23,311	7.400	£6829	0.126	Ext. dom.
Insulin lispro mix 50/50-metformin	£23,620	7.258	£7139	-0.016	Dominated
Insulin lispro mix 50 and mix 25	£23,821	6.988	£7340	-0.286	Dominated
Insulin detemir-metformin	£24,015	7.459	£7534	0.185	£40,742
Exenatide-metformin-sulfonylurea	£25,293	7.363	£1278	-0.096	Dominated
Insulin degludec-metformin	£25,661	7.450	£1646	-0.008	Dominated
Liraglutide-metformin-sulfonylurea	£31,266	7.478	£7251	0.019	£377,690

(a) Ext. dom: Extendedly dominated

Table 151: Second intensification sensitivity analysis – high baseline hypoglycaemia rates

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£17,401	7.020			
Metformin-sitagliptin-sulfonylurea	£21,925	7.007	£4525	-0.013	Dominated
NPH insulin-sulfonylurea	£22,248	6.952	£4847	-0.069	Dominated
Metformin-NPH insulin-sulfonylurea	£22,649	6.873	£5249	-0.148	Dominated
Insulin glargine-metformin-sulfonylurea	£22,837	7.032	£5437	0.012	Ext. dom.
Metformin-NPH insulin	£22,887	7.088	£5487	0.068	Ext. dom.
Insulin degludec/aspart mix-metformin	£23,410	6.973	£6009	-0.048	Dominated
Biphasic insulin aspart-repaglinide	£23,443	6.852	£6043	-0.168	Dominated
Metformin-NPH insulin-repaglinide	£23,458	7.000	£6057	-0.020	Dominated
Insulin glargine-sulfonylurea	£23,534	6.994	£6133	-0.026	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,968	6.902	£6567	-0.118	Dominated
NPH insulin	£24,175	6.912	£6775	-0.109	Dominated
Insulin glargine-metformin	£24,325	7.140	£6924	0.120	Ext. dom.
Insulin detemir-metformin	£24,825	7.201	£7424	0.180	£41,151
Insulin lispro mix 50/50-metformin	£25,480	6.977	£655	-0.224	Dominated
Biphasic insulin aspart-metformin	£25,566	6.848	£741	-0.353	Dominated
Insulin degludec-metformin	£26,363	7.203	£1538	0.003	Ext. dom.
Exenatide-metformin-sulfonylurea	£26,727	7.091	£1902	-0.110	Dominated
Insulin lispro mix 50 and mix 25	£28,960	6.614	£4135	-0.587	Dominated
Liraglutide-metformin-sulfonylurea	£32,098	7.223	£7273	0.022	£327,938

(a) Ext. dom: Extendedly dominated

4.11.4 Treatment effect adjustment for baseline HbA1c

When the original health economic model was run without the treatment effect adjustment for baseline HbA1c, the second intensification incremental results were very similar to the base-case result (see table 152).

Table 152: Second intensification sensitivity analysis – no treatment effect adjustment for baseline HbA1c

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£16,759	7.195			
NPH insulin-sulfonylurea	£21,131	7.135	£4372	-0.060	Dominated
Metformin-sitagliptin-sulfonylurea	£21,220	7.185	£4461	-0.010	Dominated
Metformin-NPH insulin-sulfonylurea	£21,343	7.065	£4585	-0.131	Dominated
Insulin glargine-metformin-sulfonylurea	£21,917	7.210	£5158	0.014	Ext. dom.
Metformin-NPH insulin	£22,025	7.265	£5266	0.070	Ext. dom.
Insulin degludec/aspart mix-metformin	£22,059	7.162	£5301	-0.033	Dominated
Metformin-NPH insulin-repaglinide	£22,141	7.187	£5382	-0.009	Dominated
Biphasic insulin aspart-repaglinide	£22,235	7.037	£5476	-0.158	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£22,580	7.091	£5822	-0.104	Dominated
Insulin glargine-sulfonylurea	£22,624	7.172	£5865	-0.023	Dominated
NPH insulin	£22,848	7.100	£6090	-0.095	Dominated
Insulin glargine-metformin	£23,661	7.313	£6902	0.118	Ext. dom.
Biphasic insulin aspart-metformin	£23,931	7.045	£7173	-0.150	Dominated
Insulin lispro mix 50/50-metformin	£24,282	7.164	£7524	-0.032	Dominated
Insulin detemir-metformin	£24,295	7.379	£7536	0.183	£41,116
Exenatide-metformin-sulfonylurea	£25,807	7.272	£1512	-0.106	Dominated
Insulin lispro mix 50 and mix 25	£25,816	6.856	£1521	-0.523	Dominated
Insulin degludec-metformin	£25,921	7.374	£1626	-0.005	Dominated
Liraglutide-metformin-sulfonylurea	£31,583	7.393	£7288	0.014	£527,150

(a) Ext. dom: Extendedly dominated

4.12 Second intensification – discussion and conclusions

All of the original health economic model analyses of second intensification treatment options should be viewed with caution, as the underlying clinical NMAs were much weaker than those supporting initial therapy and first intensification. Many NMA links were supported by single RCTs – given the base case was based on weighted averages of reported drug dosages, this will particularly impact drug costs.

In all analyses, metformin-pioglitazone-sulfonylurea was the cheapest second intensification treatment option. This was due to low drug costs, as all drugs in the treatment option were available generically. It is not immediately predictable that a treatment option that does not positively impact on HbA1c should be the most cost-effective treatment option, but the original health economic traded off HbA1c changes against weight and hypoglycaemic episodes. A strength of health economic modelling is that it explicitly trades off treatment effects, adverse events (here, weight and hypoglycaemia) and costs. The UKPDS OM1 time path equations used for HbA1c (Clarke et al. 2004) mean that long term HbA1c projections for all treatment options become very similar.

The GDG were clear that many people with type 2 diabetes may be contraindicated for prescribing pioglitazone and therefore other second intensification treatment options needed to be considered. In the decision space without metformin-pioglitazone-suflonylurea (the only pioglitazone-containing second intensification treatment option modelled) the lifetime discounted costs for most treatment options were much more similar. Weight profile assumptions and QALYs associated with treatment-related weight-change became key drivers.

In the non-pioglitazone decision space, metformin-NPH insulin was the most cost-effective treatment option at a maximum acceptable ICER of £20,000/QALY (ICER £3600/QALY compared with NPH insulin-sulfonylurea). The remaining non-injectable treatment option (metformin-sitagliptin-sulfonylurea) was extendedly dominated by NPH insulin-sulfonylurea and metformin-NPH insulin, but very close to the cost-effectibess frontier, with expected net costs that were less than those of metformin-NPH insulin. No other non-injectable treatment options, such as those combining other DPP-4 inhibitors with metformin-sulfonylurea were able to be modelled.

Neither decision spaces indicated that insulin-detemir was a cost-effective option at a maximum accepted ICER of £20,000/QALY. In the full decision space base case, insulin detemir-metformin had an ICER of £40,800/QALY compared with metformin-pioglitazone-sulfonylurea and in the non-pioglitazone decision space, insulin detemir-metformin had an ICER of £24,300/QALY compared with metformin-NPH insulin. These ICERs were driven by QALYs associated with a weight treatment effect of -0.5 kg. The GDG were not convinced such a weight-loss would be achieved in clinical practice. When an alternative weight profile was applied that removed the long-term impact of treatment-related weight gain, insulin detemir-metformin was subjected to extended dominance by NPH insulin-sulfonylurea and metformin-pioglitazone-sulfonylurea in the full base case. Conversely, if weight-loss was assumed to be regained over a longer period than 1 year, the ICER for insulin detemir-metformin compared with metformin-NPH insulin only decreased slightly to £40,300/QALY. In none of these analyses would insulin detemir-metformin be judged to represent an effective use of NHS resources; however, the GDG were not clear which weight profile was most appropriate for insulin detemir-metformin. Establishing the true weight profiles, possibly treatment-specific weight profiles, is an area for future research that would reduce the decision-making uncertainty for second intensification treatment options.

When treatment options containing 3 oral anti-diabetic agents or NPH insulin have failed to adequately control HbA1c, insulin detemir-metformin had an ICER of £10,800 compared with insulin glargine-metformin. Probabilistic analysis suggested that there was little certainty that insulin detemir-metformin should be preferred to insulin glargine-metformin (see figure 36).

For people who could not take metformin, we were only able to model 5 treatment options. NPH insulin-sulfonylurea was the cheapest treatment option, but the reported daily NPH insulin dose appeared very small. When the same daily doses were used for NPH insulin and NPH insulin-sulfonylurea, the cost and QALY differences between these two treatment options were much reduced (see table 149); however this sensitivity analysis did not take account of any changes in hypoglycaemia rates that could be associated with very different insulin doses. The GDG were concerned they had little experience using the NPH insulin-sulfonylurea treatment option and were also concerned whether, due to potential hypoglycaemia, it would be acceptable to people with type 2 diabetes who could not take metformin.

The GLP-1 agonist-metformin treatment options modelled were not cost-effective compared with metformin-pioglitazone-sulfonylurea or to metformin-NPH insulin. However, this may be because the additional conditions from the previous guideline were not able to be modelled (National Institute for Health and Care Excellence 2009). The additional conditions for exenatide-metformin-sulfonylurea required:

- an initial BMI of greater than or equal to 35 kg/m^2
- a reduction of at least 1.0% HbA1c at 6 months and
- a reduction of at least 3.0% of initial body weight at 6 months

The latter requirement was based on an assumption that such weight-loss would result in a clinically significant weight-loss of 5% of initial body weight at 12 months (National Institute for Health and Care Excellence 2009). The initial BMI for people at second intensification in our base case was 30.8 kg/m^2 (see table 20) – lower than required in condition 1 above from the previous guideline; a 5% reduction in bodyweight at 12 months from the baseline used

here would equate to −4.3 kg. The 1-year treatment effect estimates used in the original health economic model for exenatide-metformin-sulfonylurea were −0.3% HbA1c and −0.1% of initial body weight and for liraglutide-metformin-sulfonylurea were −0.7% HbA1c and +0.7% of initial body weight.

In this analysis, only 1 treatment option was modelled to have a HbA1c reduction of 1% or greater at 12 months (metformin-NPH insulin-repaglinide, -1.8 %); the greatest weight-loss modelled was -0.476 kg or 0.5% of initial body weight (insulin detemir-metformin) (see table 58). It is likely that **any** treatment option that was modelled with both a 5% weight-loss and 1% HbA1c reduction could appear cost effective, particularly if in comparison insulin-based comparisons had their costs increased to allow for increased doses due to higher BMI.

The GDG noted, in people for whom using insulin would have significant occupational implications, the use of insulin based treatment options could have a catastrophic impact on the person's quality of life. As well as underestimating the incremental cost benefits, the original health economic might be critically undervaluing the benefits of GLP-1 agonist-metformin treatment options. For these reasons, the GDG felt that if greater gains were made and greater costs would be incurred, GLP-1 agonist-metformin treatment options may still be beneficial.

Lifetime discounted QALY differences between the most effective (liraglutide-metformin-sulfonylurea) and least effective (insulin lispro mix 50 and mix 25) treatments in the base case were greater than for other therapy levels – 195 quality-adjusted life-days out of 8.2 remaining QALYs.

Whilst 20 treatment options were able to be modelled, there remained some treatment options that could not be modelled (see table 29). These particularly covered biphasic insulin treatment options and other 3 oral drug treatment options. It would have been useful to have another treatment option that only contained generic drugs to compare against metformin-pioglitazone-sulfonylurea and to be able to model other DPP 4-inhibitor-metformin-sulfonylurea treatment options.

4.13 Incremental cost–utility results when therapy intensifies to new recommendations

When the original health economic model was configured, it was necessary to make assumptions about which treatment options would be the usual choices when therapy was intensified for initial therapy and first intensification (see 3.2.1). The GDG based their assumptions on current practice and assumed metformin-sulfonylurea would be the usual choice at first intensification, followed by metformin-NPH insulin at second intensification.

However, the results of this analysis indicated that other treatment options should be considered as first-choice intensifications for initial therapy and first intensification. Metformin-pioglitazone should be used at first intensification (see 4.5.4), followed by metformin-pioglitazone-sulfonylurea at second intensification (see 4.9.4).

We re-ran our analyses using these new recommended treatment options. Lifetime discounted costs were lower when the new recommendations were modelled because of the second intensification use of a 3 OAD treatment option consisting of generic drugs instead of metformin-NPH insulin. Lifetime discounted QALYs were very slightly lower compared with base case results, due to slightly shorter survival (driven by less HbA1c improvement on metformin-pioglitazone-sulfonylurea compared with metformin-NPH at second intensification).

For initial therapy, the impact on cost-effective results was minimal. Metformin remained the dominant treatment option (see table 153). When people could not take metformin, repaglinide remained the cheapest treatment option (see table 154); when neither metformin

nor repaglinide were acceptable treatment options, pioglitazone was the cheapest treatment option (see table 155). Sitagliptin and sulfonylurea remained cost-effective treatment options for people who could not take metformin, repaglinide or pioglitazone (see table 156).

Table 153: Mean lifetime incremental cost–utility results for initial therapy – alternative intensification

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin->Met-pio->Met-pio-SU	£15,503	8.978			
Repaglinide->Met-pio->Met-pio-SU	£15,580	8.932	£76	-0.045	Dominated
Pioglitazone->Met-pio->Met-pio-SU	£15,618	8.923	£114	-0.054	Dominated
Placebo->Met-pio->Met-pio-SU	£15,704	8.859	£200	-0.119	Dominated
Sulfonylurea->Met-pio->Met-pio-SU	£15,726	8.901	£223	-0.077	Dominated
Vildagliptin->Met-pio->Met-pio-SU	£16,623	8.909	£1119	-0.069	Dominated
Sitagliptin->Met-pio->Met-pio-SU	£16,754	8.946	£1250	-0.032	Dominated

(a) Met-pio: metformin-pioglitazone
(b) Met-pio-SU: metformin-pioglitazone-sulfonylurea

Table 154: Mean lifetime incremental cost–utility results for initial therapy when metformin is not within the decision space – alternative intensification

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Repaglinide->Met-pio->Met-pio-SU	£15,580	8.932			
Pioglitazone->Met-pio->Met-pio-SU	£15,618	8.923	£38	-0.009	Dominated
Placebo->Met-pio->Met-pio-SU	£15,704	8.859	£124	-0.073	Dominated
Sulfonylurea->Met-pio->Met-pio-SU	£15,726	8.901	£146	-0.031	Dominated
Vildagliptin->Met-pio->Met-pio-SU	£16,623	8.909	£1043	-0.023	Dominated
Sitagliptin->Met-pio->Met-pio-SU	£16,754	8.946	£1174	0.013	£88,882

(a) Met-pio: metformin-pioglitazone
(b) Met-pio-SU: metformin-pioglitazone-sulfonylurea

Table 155: Mean lifetime incremental cost–utility results for initial therapy when metformin and repaglinide are not within the decision space – alternative intensification

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Pioglitazone->Met-pio->Met-pio-SU	£15,618	8.923			
Placebo->Met-pio->Met-pio-SU	£15,704	8.859	£86	-0.064	Dominated
Sulfonylurea->Met-pio->Met-pio-SU	£15,726	8.901	£108	-0.022	Dominated
Vildagliptin->Met-pio->Met-pio-SU	£16,623	8.909	£1,005	-0.014	Dominated
Sitagliptin->Met-pio->Met-pio-SU	£16,754	8.946	£1,136	0.022	£51,214

(a) Met-pio: metformin-pioglitazone
(b) Met-pio-SU: metformin-pioglitazone-sulfonylurea

Table 156: Mean lifetime incremental cost–utility results for initial therapy when neither metformin, repaglinide nor pioglitazone are within the decision space – alternative intensification

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Placebo->Met-pio->Met-pio-SU	£15,704	8.859			
Sulfonylurea->Met-pio->Met-pio-SU	£15,726	8.901	£23	0.042	£535
Vildagliptin->Met-pio->Met-pio-SU	£16,623	8.909	£897	0.008	Dominated
Sitagliptin->Met-pio->Met-pio-SU	£16,754	8.946	£1028	0.044	£23,188

(a) Met-pio: metformin-pioglitazone
(b) Met-pio-SU: metformin-pioglitazone-sulfonylurea

At first intensification, lifetime discounted costs and lifetime discounted QALYs were again reduced compared with the base case, due to the use of metformin-pioglitazone-sulfonylurea instead of metformin-NPH at second intensification. Metformin-pioglitazone remained the cheapest treatment option, followed by metformin-sulfonylurea. The DPP-4 inhibitor-metformin treatment options still appeared to exhibit a class effect that had a lowest ICER reduced from £37,800 in the base case to £32,400 for the treatment option with the lowest lifetime discounted costs (see table 157).

These analyses provided reassurance that the choice of intensification therapy had minimal impact on the incremental differences between treatment options for initial therapy and first intensification.

Table 157: Mean lifetime incremental cost–utility results for first intensification – alternative intensification

Treatment	Costs	QALYs	Incremental		
			Costs	QALYs	ICER
Metformin-pio -> Met-pio-SU	£16,046	8.154			
Metformin-sulfonylurea -> Met-pio-SU	£16,157	8.153	£112	-0.002	Dominated
Metformin- sitagliptin -> Met-pio-SU	£17,169	8.178	£1123	0.024	Ext. dom.
Metformin-vildagliptin --> Met-pio-SU	£17,173	8.189	£1127	0.035	£32,404
Linagliptin-metformin -> Met-pio-SU	£17,202	8.189	£29	0.000	Ext. dom.
Exenatide-metformin -> Met-pio-SU	£18,717	8.191	£1545	0.002	Ext. dom.
Liraglutide-metformin -> Met-pio-SU	£19,466	8.224	£2293	0.035	£65,515

(a) Ext. dom: extendedly dominated
(b) Met-pio: metformin-pioglitazone
(c) Met-pio-SU: metformin-pioglitazone-sulfonylurea

5 Discussion

An original health economic model has assessed the cost effectiveness of pharmacological blood glucose-lowering therapies to control blood glucose levels in people with type 2 diabetes. The original health economic model had strengths and limitations and has raised a number of further issues in the health economic modelling of type 2 diabetes drugs.

5.1 Health economic model strengths

The original health economic model had a number of strengths and improvements over previous guidelines and published CUAs.

The same model was used to incrementally assess a large of number of treatment options at 3 stages of disease progression. Previously published CUAs have not included as many comparators. Somewhat surprisingly, this is the first CUA to analyse initial therapy for type 2 diabetes in a setting relevant to the NHS.

Our original health economic model took its treatment effects from a related clinical evidence review and a series of NMAs. We modelled the correlations between treatment effects for each therapy level, which previous CUAs have not done, thereby providing a much more robust reflection of the evidence-base.

Primarily as a result of all being based at least in part on UKPDS RCT risk equations, virtually all health economic models use annual cycles. However, previous CUAs have sometimes used treatment effect data from RCTs of less than 1 year (see 2.2). For initial therapy and first intensification, the original health economic model used HbA1c and weight treatment effects from 1-year NMAs and thus truly reflected 1-year treatment effects.

The original health economic model was one of the first to model treatment dropouts due to intolerance. In a recent review of liraglutide CUAs, this was noted as a key issue (Zueger et al. 2014). Given a key aim of health economic modelling is to reflect reality, it seemed important to reflect differences between treatments in treatment dropouts due to intolerance. Indeed, rates varied between less than 1% and over 80% at the extremes and between 4% and 15% for most therapy levels (see 3.5.4).

All health economic models rely on baseline data for their modelled cohorts. The original health economic model used baseline data that represented a substantial step forward from previous analyses (see 3.3). Baseline data from clinical practice based on a large UK source were used to select all but 1 input. Different data were used for each therapy level, accurate data on pre-existing complications were sourced and differential risk factor data at both the decision point and at diabetes diagnoses were used. The original health economic model appears to be the first published CUA to have considered and modelled correlations between baseline characteristics. By generating samples of 50,000 people for each model run, population heterogeneity was accurately modelled in base-case results and sensitivity analyses.

The previous guideline (National Institute for Health and Care Excellence 2009) used assumed daily dosages to cost treatment options. The original health economic model maintained a link between cost and magnitude of treatment effect by using weighted daily drug doses from the included RCTs (see 3.8.2). Also, the original health economic accurately inflated UKPDS long term outcome costs, avoiding potential rounding errors (see 3.8.1).

Hypoglycaemia utility decrements have been applied differently to previous guidelines and published CUAs (see 3.10.4). We believe that the methods we have employed are more in line with the source paper, but is likely to have reduced the QALYs lost to hypoglycaemic episodes. This implies that existing CUAs that applied hypoglycaemia utility decrements directly may be somewhat biased in favour of treatments with lower hypoglycaemia rates. If

done in the manner used in previous guidelines and CUAs, applying the hypoglycaemia utility decrements as reported in Currie et al. (2006) implies hypoglycaemic events have an impact similar to having an MI.

We believe that the original health economic model represents one of the first thorough and fully valid PSAs for type 2 diabetes modelling (see 3.11.1). Indeed, the previous guideline was unable to produce a PSA (National Institute for Health and Care Excellence 2009). The modular approach allowed the separate consideration of population heterogeneity, stochastic uncertainty and parameter uncertainty. This included integrated probabilistic analysis of the underlying UKPDS risk equation parameters and correlated treatment effects.

Overall, the original health economic provided a more accurate reflection of detailed clinical evidence and addressed a number of issues apparent in previous type 2 diabetes modelling.

5.2 Health economic model limitations

However, the original health economic model was not without limitations. Some limitations were specific to the original health economic model, but some were generic to all type 2 diabetes health economic models.

5.2.1 Limitations specific to the original health economic model

Whilst the original health economic model included more treatment options than any previous analysis, it could not include all comparators within the decision space. Only treatment options for which the minimum dataset were available could be modelled (see 3.4). This limitation had greatest impact at first intensification, where all the treatment options contained metformin and no meglitinide treatment options could be modelled in the base case.

One reason that not all treatments could be modelled was the strict use of 1-year treatment effect data. Whilst this was a strength, it meant that HbA1c treatment effect data for 3 and 6 months could not be included in the original health economic model. This means the results do not fully reflect the benefits of treatment options with greater short-term than long-term treatment effects, but overall represented a strength that treatment effects were properly incorporated in the original health economic model. Similarly, not using treatment effect data from 2 years or more in base case may bias against treatment options with greater long-term treatment effects, but reported longer-term data are sparse. Mathematically and clinically valid methods for extrapolating less than 1 year HbA1c data to 1 year for each treatment option were not found and could be a focus of future research.

Due to the sparseness of the NMA, HbA1c and weight data for second intensification treatment options were modelled at up to 1 year rather than at 1 year. Few treatments could have been modelled if treatment effect at 1 year only was used. However, using treatment effect data up to 1 year seemed no worse than using data from a point at less than 1 year and extrapolating to 1 year.

The original health economic model was the first analysis to systematically model treatment dropouts due to intolerance (see 3.2.5). This introduced a number of necessary modelling assumptions. Firstly, the GDG assumed that people with type 2 diabetes would be intolerant of no more than 2 treatment options at a given therapy level and would not be intolerant of the third treatment option. The clinical accuracy of this assumption is not known; the GDG indicated that people may intensify treatment rather than switch within a therapy level but it was not possible to model such a scenario. Secondly, for modelling simplicity, the original health economic model assumed that intolerances did not transfer between therapy levels. This is unlikely to be true – for instance a person who was intolerant of metformin initial therapy is unlikely to then take a metformin based first intensification treatment option. However, to model such memory would have been burdensome. Thirdly, treatment dropouts due to intolerance were assumed to only occur in the first year of a treatment option. In

reality, rates may decay or change over time (even within the first year). Fourthly, second intensification switches were limited by not considering the use of basal-bolus insulin regimes. It was decided that treatment switches should be taken treatment options within the the available clinical evidence rather than from outside sources.

The baseline characteristic data used in the original health economic represented a step change compared with previous analyses but were not without limitations. The selection of first- and second-intensification data was based on specific type 2 diabetes duration timepoints (see 3.3.2) rather than directly reflecting people requiring intensification of treatment at the time they required it. However, the duration timepoints were based on the included RCTs and seemed appropriate to the GDG. Ethnicity data had to be taken from an alternative source and this limited the correlation data that were available. To ensure the correlation matrices remained positive-definite, correlations were based on the subset of people who had all variables recorded, rather than the entire dataset. On balance, however, we are certain that the benefits of the baseline characteristic dataset used far outweighed the limitations.

Hypoglycaemia base rates were sourced from outside the included RCTs (see 3.5.4). The use of a hierarchical data selection model meant that whilst the relativities between RCT arms could be preserved, it was not appropriate to calculate a pooled baseline hypoglycaemia rate across all RCTs and all hypoglycaemia categories and data were too sparse to calculate baseline rates for specific hypoglycaemia categories. Using epidemiological baseline rate data put hypoglycaemaia at odds with other modelled outcomes. Such baseline data were not found for weight or treatment dropouts due to intolerance; using epidemiological data for HbA1c would not have allowed us to explore the relationship between baseline HbA1c and HbA1c treatment effect.

The hypoglycaemia base rates sourced from epidemiological data were not ideal matches to the decision problem, but represented the best available data according to prior defined criteria. It was necessary to assume which second intensification therapy the baseline rate should be applied to; the percentage of severe hypoglycaemic episodes was assumed to be the same across all treatment options. An increase in the number of treatment options that could be modelled was traded off against the use of a hierarchical data selection model, the validity of which was found to be reasonable (see 3.5.4.4).

Drug doses were based on weighted average doses from the included RCTs (see 3.8.2). The weighting was purely based on the number of people within each arm and may have been improved with a more formal analysis, including some measure of dose dispersion. However it is unlikely this was reported in all RCTs and using weighted average doses was an improvement on previous analysis.

Drug costs were based on the cheapest pack size listed (cost per mg) and no combination tablets were considered (see 3.8.3). As is usual in NICE guidelines and like all other published CUAs, drug costs were taken as current and no attempt was made to consider future potential cost changes when patent periods end.

Where RCTs reported insulin dose per kilogram bodyweight but did not report mean bodyweight, the mean bodyweight from the baseline data were used – this may or may not be accurate. Insulin costs were not increased over time with increasing bodyweight as the impact of such costs was thought to be minimal. However, given the influence of different weight profile assumptions on cost effectiveness results, future analyses may wish to include increasing insulin costs in line with increasing bodyweight.

It may be argued that some double-counting of insulin initiation costs occurred in the original health economic model, as people who switched from their first insulin-based treatment option due to intolerance incurred insulin initiation costs again on their switched treatment. This may have introduced a slight bias against insulin based treatment options with higher

dropout rates. However, the switched treatment would probably also need some initiation and titration and thus incur some initiation costs.

Whilst weighted average costs of insulin products, needles, SMBG strips and SMBG lancets were based on usage (prescriptions issued, see 3.9), prescription data were not specific to type 2 diabetes. However, the GDG were content that usage of affected products is unlikely to differ between people with type 2 diabetes and people with type 1 diabetes and preferred to use a weighted average of current usage than the cost of a particular brand or an assumption.

5.2.2 Limitations not specific to the original health economic model

All health economic modelling of type 2 diabetes relies at least in part on equations from the UKPDS RCT that use short-term biomarkers to predict long-term outcomes. Some limitations of the UKPDS RCT for modelling type 2 diabetes have already been discussed (see 3.1). Of general concern to type 2 diabetes modelling are the UKPDS RCT being based on newly diagnosed people with type 2 diabetes only and the age of the UKPDS RCT. The age of the UKPDS RCT has a particular impact on costs, as care patterns will have changed considerably since the UKPDS long-term outcome costs were calculated. The publication and potential future use of updated UKPDS RCT costs (Alva et al. 2014b) may partly alleviate this issue.

UKPDS RCT long-term outcome costs were based on the average participant, a 59-year-old male (see 3.8.1). It is probable that costs could differ for female or older people but this has not been explored. In an analysis such as this with different populations, such cost differences may be important.

Similarly, UKPDS RCT long-term outcome utilities were also based on a 59 year old male (see 3.10.1). Different outcomes may impact different ages and genders differently – Clarke et al. (2002) found gender but not age to be a significant variable. Also, no consideration has been given to reducing baseline utility with increasing age (Dolan et al. 1996), either as the original health economic model progresses or for different starting populations. As UKPDS RCT long-term outcome utility decrements were additive, a person with lower starting utility would lose a greater proportion of their utility when complications occur. Differences between QALYs are generally small in type 2 diabetes CUAs; neither different baseline utilities nor reducing utility over time appear to have been considered. Again, recently updated UKPDS RCT utilities (Alva et al. 2014a) may be applicable in future analyses.

The annual UKPDS RCT equations are a key driver in the annual model cycles of virtually all type 2 diabetes models. As previously discussed, this leads to the use of sub-1-year data at 1 year (see 2.2) or, as in the case of our original health economic model, leads to the discarding of sub-1-year data (see 3.2.4).

Treatment-related weight-changes are becoming increasingly key in decisions over the cost effectiveness of type 2 diabetes drugs. However, there is no clear agreement over which weight profiles are most appropriate to model. Treatment-related weight-loss and gain may or may not have different profiles and it may be possible that different treatment options have different weight profiles to each other. This analysis has tested a variety of weight profile assumptions (see 3.11.2.2) and found them to influence cost-effectiveness results. Evidence on the long-term impact of treatment-related weight-change, potentially on a treatment option specific basis, would reduce a key area of uncertainty in health economic modelling of type 2 diabetes.

Hypoglycaemia rates are assumed to remain constant throughout the lifetime of nearly all published CUAs. There is some evidence that rates may change over time (Wright et al. 2006) and the impact of such changes could impact cost effectiveness results.

Utility decrements for treatment-related weight-changes (see 3.10.3) and hypoglycaemic episodes (see 3.10.4) were, to different extents, key model drivers. The utility values used here are widely used in published CUAs but are taken from small, methodologically limited studies. A recent systematic review of utility values used in diabetes modelling illustrated the range of values available and the lack of clarity over the true population values (Beaudet et al. 2014).

It is generally assumed that the quality of life impacts of treatment-related weight-change are linear (above a baseline). It is conceivable that treatment-related weight-gain and loss have differing utility impacts and that, like implemented for hypoglycaemic episodes in this analysis (see 3.10.4), utility decrements differ by weight-change magnitude. There is also potential evidence that baseline body weight influences the magnitude of utility changes – for instance, weight-loss may incur a greater utility gain for people with higher starting weights (Matza et al. 2007).

The limitations that were not specific to the original health economic model represent some potentially serious limitations. It should be acknowledged that if these were addressed, this and other CUAs might reach different cost-effectiveness conclusions.

5.3 Comparison with other cost–utility analyses

The original health economic has found different results to the previous guideline (National Institute for Health and Care Excellence 2009). Whilst the previous guideline used UKPDS OM1, it employed a number of structural differences to the original health economic model. The previous guideline:

- Modelled intensification to basal-bolus insulin regime (with an assumed HbA1c treatment effect of -0.5%)
- Employed treatment-related weight-change treatment effects only at the beginning of treatment and did not model weight profiles
- Used average daily drug dosages and did not model dose titration
- Included a nausea treatment effect for some treatment option comparisons and only modelled severe (and sometimes nocturnal) hypoglycaemia
- Modelled 250,000 iterations of 1 person
- Weight, nausea and hypoglycaemia utilities and drug costs were only modelled deterministically
- No PSA was reported

The previous guideline undertook 5 pairwise comparisons, of which 3 were contained in the second intensification decision space for the current analysis. All treatments in the previous guideline were combined with metformin-sulfonylurea; in the current analysis these metformin-sulfonylurea based treatment options were not found to be cost-effective and it was the metformin-only treatment options that were of interest. Treatment effects modelled varied between comparisons; table 158 shows the absolute HbA1c and weight treatment effect differences used by the previous guideline and this analysis. It can be seen that different treatment effects were modelled in some instances, particularly for insulin detemir versus NPH insulin. However, the current analysis was for insulin detemir-metformin rather than insulin detemir-metformin-sulfonylurea and this could have affected the weight-change treatment effect.

There were also differences in the baseline characteristics (see 3.3), costs (see 3.8.2) and utilities (see 3.10) used in the previous guideline compared with our original health economic model.

Table 158: Treatment effects modelled in CG87 and current analysis

Comparison	HbA1c		Weight	
	CG87	Current Analysis	CG87	Current Analysis
Exenatide v insulin glargine	No difference (both -1.1%)	-0.15% in favour of exenatide	-4.1 kg in favour of exenatide	-4.1 kg in favour of exenatide
Insulin glargine v NPH insulin	No difference	-1.38% in favour of insulin glargine	-0.28 kg in favour of insulin glargine	-0.17 kg in favour of NPH insulin
Insulin detemir v NPH insulin	-0.08% in favour of NPH insulin	-0.80% in favour of insulin detemir	-1.2 kg in favour of insulin detemir	-4.2 kg in favour of insulin detemir

(a) All treatments included metformin-sulfonylurea, with the exception of insulin detemir which in the original health economic model was only analysed with metformin
(b) CG87 treatment effects for severe hypoglycaemia and nausea not shown

Given the array of structural, treatment effect and input differences, it would be unlikely that the previous guideline would produce the same results as the original health economic model. Indeed, this analysis has found the opposite results for all 3 comparisons from the previous guideline (see table 159), the reasons for which are given above. It should be remembered that the 'results' shown for the original health economic model are taken out of context as they sit within a much wider decision space and linked NMA and are the mean results from 1000 probabilistic iterations. The results shown here for the original health economic analysis should not be taken as justification for the use or recommendation any of the treatments listed.

Table 159: Comparison of ICERs from CG87 and current analysis

Comparison in previous guideline	Previous guideline (CG87)		Original health economic model	
	ICER	Result	ICER	Result
Exenatide v insulin glargine	£19,995	Exenatide cost effective compared with insulin glargine, but only if weight lost	£52,349	Insulin glargine cost effective compared with exenatide
Insulin glargine v NPH insulin	£320,029	NPH insulin cost effective compared with insulin glargine	£5671	Insulin glargine cost effective compared with NPH insulin
Insulin detemir v NPH insulin	£417,625	NPH insulin cost effective compared with insulin detemir	£7486	Insulin detemir cost effective compared with NPH insulin

(a) All treatments included metformin-sulfonylurea, with the exception of insulin detemir which in the current analysis was only analysed with metformin
(b) Previous guideline results shown were for a male with BMI of 30 and pre-existing complications, see section 2.6.2 in CG87
(c) Results from current analysis were derived using pairwise comparisons from full incremental analysis (see table 138). ICERs shown may differ slightly from those calculated via table 138 due to rounding in table 138

Similarly, it is hard to compare the results of the original health economic model to the existing literature reviewed in section 2. Existing CUAs used a plethora of different assumptions and inputs to produce sometimes diametrically opposed results. No CUAs were found for initial therapy (see 2.2.1), meaning that the results presented here – particularly for people who could not take metformin – are a real addition to the existing literature. The 2 CUAs found for first intensification (see 2.2.2) both modelled treatment effects for SBP and cholesterol, in addition to HbA1c, weight and hypoglycaemia and used larger utility decrements for weight and hypoglycaemia than the current original health economic model. CUAs found for second intensification (see 2.2.3) chose to model a variety of treatment effects from hypoglycaemia only to HbA1c, SBP, cholesterol, weight, hypoglycaemia and nausea. It was noticeable that results for both intensifications were frequently driven by non-HbA1c factors.

5.4 Comment

The original health economic model had a number of strengths and made a number of improvements on previous guidelines and published CUAs. The modelling of much bigger decision spaces allowed more detailed incremental analyses than previously undertaken; baseline input data (including correlations between variables) were a step-change in type 2 diabetes modelling. A number of decisions were implemented that led to more accurate modelling of underlying data (treatment correlations, annual data, dropouts, hypoglycaemia utility) and the production of a thoroughgoing PSA. All these improvements were to aid better decision making with robust exploration of uncertainty.

At all therapy levels, results were sensitive to different weight-profile assumptions. When treatment-related weight-loss was assumed to rebound gradually rather than immediately, ICERs for weight-losing treatment options were reduced. When treatment-related weight-gain was assumed to rebound immediately, ICERs for weight-gaining treatment options were reduced. An assumption of gradual loss (rather than immediate or never) of treatment-related weight-gain was not tested, but it is possible to extrapolate the likely overall impact from existing sensitivity analyses. Establishing what weight profiles should be modelled would seem to be a key information need for future type 2 diabetes modelling.

Lifetime discounted QALY differences between treatment options were small – the equivalent of less than 46 days in perfect health for initial therapy and less than 26 days for first intensification with a slightly greater difference of 195 days for second intensification. Given the small differences and large amounts of uncertainty within the original health economic model, in tables, costs have been reported to the nearest pound and QALYs to enough decimal places to differentiate between treatment options. In the text, ICERs have only been reported to the nearest £100 – it seemed incongruous and unhelpful to decision making to discuss ICERs to any greater degree of accuracy.

Within the small QALY differences, UKPDS long-term outcomes accounted for between 19% (first intensification) and 31% (second intensification) of differences. Whilst discounting is designed to take account of time preferences, it is increasingly apparent that the primary drivers of decision making for type 2 diabetes drugs are short-term outcomes. The growing array of existing type 2 diabetes models are complex, long-term models where subtle differences in inputs or assumptions can impact outcomes in ways that are not always obvious.

Many RCTs are done on a 'treat to target' basis, meaning they are not designed to find differences in HbA1c reductions but in, for example, percentages of people achieving particular HbA1c target values. Existing type 2 diabetes models are not set up to directly model such targets. If treatment options can be shown to achieve equivalent HbA1c levels, then the value of using long-term computationally burdensome modelling is questionable. However, very few previously published CUAs assume equivalence of the HbA1c impact (Zueger et al. 2014). Perhaps more transparent models focusing on the impacts of shorter-term outcomes such as weight and hypoglycaemia would be of more use to decision makers – outcomes that do not have proven long-term benefits but drive model results (Asche et al. 2014). Such an approach would move type 2 diabetes modelling away from its reliance on the UKPDS RCT with all its inadequacies for this purpose, but would require more robust cost and utility estimates for such outcomes than are currently available.

In this respect, the original health economic model has followed the same path as all other health economic analyses of type 2 diabetes drugs, perpetuating a number of assumptions and even justifying certain decisions on the basis of previously made decisions or values used. However, we suggest that the time for a broader debate, questioning some of the self-perpetuating conventions of type 2 diabetes health economic modelling may be overdue. Complicated, slow-running patient-level models such as the one used in our analysis are ubiquitous in the economic analysis of type 2 diabetes. The complexity and/or computational

burden of these models is frequently cited to justify the absence of sophisticated analysis, especially as regards the challenge of producing valid probabilistic analysis. We contend that our analysis has met this challenge more completely than any previous CUA; however, this was only achieved with very extensive computing resource and extended run-times, and the modelling solution we adopted was necessarily intricate.

Model run times were hugely dependent on hardware and available resources. The original health economic model was primarily run on a group of 9 virtual 32-bit Windows machines, each with 2 2.9 Ghz central processing unit (CPU) cores and 3 GB of random access memory (RAM) assigned. UKPDS OM1 required the use of the older 32-bit Windows operating system, rather than a more recent 64-bit operating system. On these computers, each probabilistic iteration of 50,000 people and 100 loops took around 3.5 hours to run for initial therapy and first intensification (each with 7 treatment options compared) and around 10 hours for second intensification (taking longer due to the higher number (20) of treatment options compared). Sensitivity analyses based on 50,000 people and 1000 loops took around 17.5 hours for initial therapy and first intensification and around 50 hours for second intensification.

We believe it is sensible to question whether the simplifications that would be necessary to adopt a less cumbersome modelling approach would be justifiable, given the very significant extra flexibility that could be expected. In many ways, the models that are used in type 2 diabetes are among the most sophisticated in health economics; conversely, it is remarkable that useful PSAs remain the exception in the field, rather than the overwhelming rule. We take the view that the trade-off between theoretical face-validity and analytical agility could fruitfully be explored.

A useful exploration of whether such short-term modelling approaches would be more valuable than their existing longer-term counterparts would be a thoroughgoing value of information analysis. Value of information analysis relies on a full PSA, which is presumably the limiting factor for type 2 diabetes research currently. It seems inconceivable that the NHS spends over £1m every hour on diabetes care (Hex et al. 2012) and yet no value of information analysis has been undertaken to direct future research.

5.5 Areas for future research

This analysis has highlighted a number of areas of uncertainty within type 2 diabetes modelling that would benefit from further research. It should be noted that these suggestions are made with the express aim of reducing future decision making uncertainty, rather than to further complicate an already complicated modelling field. In this light, value of information analysis (see 5.4) would be particularly useful to guide future research, but may be prohibitively computationally demanding if based on the kind of patient-level modelling used in our analysis and almost all other type 2 diabetes CUAs.

Further clinical research to provide data that would allow more treatments to be modelled would reduce decision making uncertainty. Non-metformin-based treatment options at first intensification and other 3-OAD options at second intensification were gaps due to a lack of clinical data in this analysis.

Models that rely primarily on the UKPDS risk equations necessarily have annual cycles. However, many type 2 diabetes RCTs have durations or intermediate data points of less than 1 year. There does not currently appear to be any methods to extrapolate outcomes (HbA1c in particular) from timepoints of less than 1 year to 1 year and many existing CUAs have merely assumed that a shorter timepoint data can be used at 1 year. Developing such methods would have enabled more treatment options to be modelled and potentially useful less data to be discarded.

Alternatively, models that can analyse data in less than 1 year cycles could be developed. This would allow alternative consideration of treatments such as sulfonylurea which appeared to have more immediate HbA1c impacts.

Treatment-related weight-change was a key driver of model results in this and previous analyses. There are a number of uncertainties regarding treatment-related weight-change that, if researched, would substantially reduce the decision making uncertainty for future type 2 diabetes cost–utility analyses. The speed and duration of treatment-related weight-change is unclear and could be different for different treatment options or when people stop, switch or intensify therapies. Also, the utility associated with weight-change has not been well studied – utility changes could differ by starting weight and changes for weight gain and weight loss may not be the same.

A key feature of recent type 2 diabetes CUAs is that short-term utility decrements rather than long-term complication utility decrements have tended to drive modelled results. Short-term and long-term utility decrements are taken from different sources. It would be useful to study both short-term and long-term utility decrements in the same research, in order to better assess their relative magnitudes. Also, considering underlying disease severity would be useful – people with type 2 diabetes with poorer health may place less emphasis on short-term utility changes.

Existing analyses have assumed that hypoglycaemia rates remain constant over time, but it may be that hypoglycaemia rates reduce (as people adapt to treatment options) or increase (as HbA1c control worsens). For this reason, additional research on longitudinal trend in hypoglycaemia may be illuminating.

UKPDS costs (Clarke et al. 2003) do not differentiate by age, gender or disease severity (see 3.8.1). It could be that costs differ by these factors and this may impact the cost-effectiveness of treatment options in different populations. A strength of this analysis was the modelling of individual-level heterogeneity that could be adapted to model long-term complication costs that varied by age and gender. The model structure could give true population mean estimates of costs and QALYs, rather than having to rely on sub-group analysis (Vemer et al. 2014).

If long-term modelling of type 2 diabetes is to continue, incorporating the updated UKPDS risk equations, cost and utilities would begin to address some of the concerns raised about the age of the existing risk equations, costs and utilities (see 3.1). However, the similarity of HbA1c outcomes in recent treatment options and preponderance of short-term outcomes driving model results suggest that clearer modelling alternatives to the existing long-term models could be strongly considered.

Appendix F.1: List of excluded CUAs

Table 160: List of excluded CUAs with reasons for exclusion, key finding and sponsor

Reference	Reason for exclusion	Key finding	Sponsor
Ali,M., White,J., Lee,C.H., Palmer,J.L., Smith-Palmer,J., Fakhoury,W.. Therapy conversion to biphasic insulin aspart 30 improves long-term outcomes and reduces the costs of type 2 diabetes in Saudi Arabia. Journal of Medical Economics 2008;11(4):651-70.	Not UK	Conversion to BIAsp 30 from HI was projected to improve life expectancy and quality-adjusted life expectancy while reducing lifetime direct medical costs	Novo Nordisk (maker of BIAsp 30)
Beale,S. Bagust. Cost-effectiveness of rosiglitazone combination therapy for the treatment of type 2 diabetes mellitus in the UK. PharmacoEconomics 2006;21(1):S21-34	Comparator not in scope (rosiglitazone)	Rosiglitazone in combination with metformin is a cost-effective treatment in the UK for both obese and overweight patients failing on metformin monotherapy, compared with conventional therapy using metformin in combination with sulfonylurea	GlaxoSmithKline (maker of rosiglitazone)
Bergenheim,K., Williams,S.A., Bergeson,J.G., Stern,L.. US cost-effectiveness of saxagliptin in type 2 diabetes mellitus. American Journal of Pharmacy Benefits.4 (1) (pp 20-28), 2012.	Not UK	Addition of saxagliptin to metformin is associated with improvement in QALYs when considering cost and disutility due to treatment side effects. Cost effectiveness is within acceptable cost-effectiveness threshold in the United States	AstraZeneca (maker of saxagliptin)
Brandle,M. & Azoulay,M.. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 diabetes in Switzerland. International Jrnal of Clinical Pharmacology & Therapeutics 2007;45(4):203-20	Not UK	Insulin glargine proved to be cost-effective and represents good to excellent value for money compared to NPH insulin	Sanofi (maker of insulin glargine)
Brandle,M. & Azoulay,M.. Cost-effectiveness of insulin glargine versus NPH insulin for the treatment of Type 2 diabetes mellitus, modeling the interaction between hypoglycemia and glycemic control in Switzerland. International Journal of Clinical Pharmacology & Therapeutics 2011;49(3):217-30.	Not UK	The base case and sensitivity analyses demonstrated that insulin glargine proved to be cost-effective with respect to accepted willingness to pay thresholds	Sanofi (maker of insulin glargline)
Brandle,M., Erny-Albrecht,K.M., Goodall,G., Spinas,G.A., Streit,P.. Exenatide versus insulin glargine: a cost-effectiveness evaluation in patients with Type 2 diabetes in Switzerland. International Journal of Clinical Pharmacology & Therapeutics 2009;47(8):501-15	Not UK	Based on current standards exenatide would be a cost-effective treatment alternative to insulin glargine in Switzerland for Type 2 diabetes patients inadequately controlled on oral therapy	Eli Lilly (maker of exenatide)

Reference	Reason for exclusion	Key finding	Sponsor
Brandle,M., Goodall,G., Erny-Albrecht,K.M., Erdmann,E.. Cost-effectiveness of pioglitazone in patients with type 2 diabetes and a history of macrovascular disease in a Swiss setting. Swiss Medical Weekly 2009;139(11-12):173-84.	Not UK	Pioglitazone is likely to be a cost-effective treatment option in the Swiss setting over patient lifetimes	Takeda (maker of pioglitazone)
Brown,R.R. Cost-effectiveness and clinical outcomes of metformin or insulin add-on therapy in adults with type 2 diabetes. Am J Health Syst Pharm Dec 1, 1998 55:S24-S27	RCT	Metformin was more cost effective than insulin when primary therapy with a sulfonylurea failed	Not stated
Cameron,C.G.. Cost-effectiveness of insulin analogues for diabetes mellitus. CMAJ Canadian Medical Association Journal 2009;180(4):400-07.	Not UK	Routine use of insulin analogues, especially long-acting analogues in type 2 diabetes, is unlikely to represent an efficient use of finite health care resources	Independent
Charles,M., Minshall,M.E., Pandya,B.J., Baran,R.W.. A cost-effectiveness analysis of pioglitazone plus metformin compared with rosiglitazone plus metformin from a third-party payer perspective in the US (Provisional abstract). Current Medical Research and Opinion 2009;25(6):1343-53.	Comparator not in scope (rosiglitazone)	Pioglitazone plus metformin, when compared to rosiglitazone plus metformin, was a dominant treatment strategy within the US payer setting	Takeda (maker of pioglitazone)
Chirakup,S et al. Cost-effectiveness analysis of thiazolidinediones in uncontrolled type 2 diabetic patients receiving sulfonylureas and metformin in Thailand. Value in Health Special Issue: Pharmacoeconomics and Outcomes Research in Asia. Volume 11, Issue Supplement s1, pages S43–S51, March/April 2008	Not UK	In type 2 diabetic patients who cannot control their blood glucose under the combination of sulfonylurea and metformin, the use of pioglitazone 45 mg fell in the cost-effective range recommended by World Health Organization (one to three times of GDP per capita) on average, compared to rosiglitazone 8 mg	Thailand Research Fund (independent)
Diaz,de Leon-Castaneda, Altagracia-Martinez,M., Kravzov-Jinich,J., Cardenas-Elizalde,Mdel R., Moreno-Bonett,C.. Cost-effectiveness study of oral hypoglycemic agents in the treatment of outpatients with type 2 diabetes attending a public primary care clinic in Mexico City. Clinicoeconomics & Outcomes Research 2012;4():57-65.	Not UK	Glibenclamide is the most cost-effective treatment for the present study outpatient population diagnosed with type 2 diabetes in the early stages	Not stated
Elgart,J.F., Caporale,J.E., Gonzalez,L., Aiello,E., Waschbusch,M.. Treatment of type 2 diabetes with saxagliptin: a pharmacoeconomic evaluation in Argentina. Health Economics Review 2013;3(1):11.	Not UK	According to the criteria proposed by the Commission on Macroeconomics and Health, the use of the combination SAXA+MET is highly cost-effective in Argentina	Bristol Myers Squibbs (maker of saxagliptin)

Reference	Reason for exclusion	Key finding	Sponsor
Erhardt,W., Bergenheim,K., Duprat-Lomon,I.. Cost effectiveness of saxagliptin and metformin versus sulfonylurea and metformin in the treatment of type 2 diabetes mellitus in Germany: a Cardiff diabetes model analysis. Clinical Drug Investigation 2012;32(3):189-202.	Not UK	The study demonstrated improved outcomes with saxagliptin at a cost that would likely be considered acceptable in the German setting	AstraZeneca, Bristol Myers Squibbs (makers of saxagliptin)
Ericsson,A., Pollock,R.F., Hunt,B.. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. Journal of Medical Economics.16 (12) (pp 1442-1452), 2013.	Not UK	Use of degludec is likely to be cost-effective compared to glargine from a societal perspective in T1D, T2-BOT, and T2-BB in Sweden over a 1-year time horizon	Novo Nordisk (maker of insulin degludec)
Evans,M., Wolden,M., Gundgaard,J., Chubb,B.. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin - from the UK healthcare cost perspective (Provisional abstract). Diabetes Obesity and Metabolism 2013;(4):epub.	Not long term model	For patients with T2DM who are considered appropriate for treatment with a basal insulin analogue, IDeg is a cost-effective treatment option compared with IGlar	Novo Nordisk (maker of insulin degludec)
Fonseca,T., Clegg,J., Caputo,G., Norrbacka,K., Dilla,T.. The cost-effectiveness of exenatide once weekly compared with exenatide twice daily and insulin glargine for the treatment of patients with type two diabetes and body mass index >=30 kg/m2 in Spain. Journal of Medical Economics.16 (7) (pp 926-938), 2013	Not UK	EQW is a cost-effective option for the treatment of T2DM patients in Spain for patients with a BMI > 30 kg/m2 considering a willingness-to-pay threshold of 30,000 per QALY gained	Eli Lilly (maker of exenatide)
Gaebler,J.A., Soto-Campos,G., Alperin,P., Cohen,M., Blickensderfer,A., Wintle,M., et al. Health and economic outcomes for exenatide once weekly, insulin, and pioglitazone therapies in the treatment of type 2 diabetes: a simulation analysis. Vascular Health & Risk Management 2012;8:255-64.	Not UK	ExQW treatment may decrease rates of cardiovascular and some microvascular complications of T2DM. Increased QALYs, and decreased costs were also projected	Amylin (maker of exenatide)
Gao,L. & Zhao,F.L.. Cost-utility analysis of liraglutide versus glimepiride as add-on to metformin in type 2 diabetes patients in China. International Journal of Technology Assessment in Health Care 2012;28(4):436-44.	Not UK	When the UK cost of liraglutide was discounted by 38 percent, liraglutide would be a cost-effective option in China from the healthcare system perspective using the 3X GDP/capita per QALY as the WTP threshold	Not stated
Goodall,G. et al. Cost-effectiveness of exenatide versus insulin glargine in Spanish patients with obesity and type 2 diabetes mellitus. Endocrinol Nutr. 2011 Aug-Sep;58(7):331-40	Not UK	Considering a willingness-to-pay threshold of €30,000 per QALY gained in the Spanish setting, exenatide represents an efficient option in comparison with IG	Eli Lilly (maker of exenatide)

Reference	Reason for exclusion	Key finding	Sponsor
Goodall,G., Jendle,J.H., Valentine,W.J., Munro,V., Brandt,A.B., Ray,J.A., et al. Biphasic insulin aspart 70/30 vs. insulin glargine in insulin naive type 2 diabetes patients: modelling the long-term health economic implications in a Swedish setting. International Journal of Clinical Practice 2008;62(6):869-76.	Not UK	Biphasic insulin aspart 70/30 treatment was associated with improved clinical outcomes and reduced costs compared with insulin glargine treatment over patient lifetimes.	Novo Nordisk (maker of Biphasic insulin aspart 70/30)
Granstrom,O., Bergenheim,K., McEwan,P., Sennfalt,K.. Cost-effectiveness of saxagliptin (Onglyza) in type 2 diabetes in Sweden. Primary care diabetes 2012;6(2):127-36.	Not UK	The addition of saxagliptin to metformin is associated with improvements in quality-adjusted life years compared with SU in patients with type 2 diabetes. Saxagliptin treatment is a cost-effective treatment alternative for type 2 diabetes in patients not well-controlled on metformin alone	AstraZeneca (maker of saxagliptin)
Grima,D.T. & Thompson,M.F.. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics 2007;25(3):253-66.	Not UK	The cost-effectiveness ratios for insulin glargine use for type 1 and 2 diabetes provide evidence for its adoption from a Canadian healthcare payer perspective	Sanofi (maker of insulin glargine)
Grzeszczak,W., Czupryniak,L., Kolasa,K., Sciborski,C., Lomon,I.D.. The cost-effectiveness of saxagliptin versus NPH insulin when used in combination with other oral antidiabetes agents in the treatment of type 2 diabetes mellitus in Poland. Diabetes Technology & Therapeutics 2012;14(1):65-73.	Not UK	Saxagliptin in combination with MET or SU is likely to represent a cost-effective treatment option in Polish patients with type 2 diabetes failing first-line treatment	AstraZeneca, Bristol Myer Squibbs (makers of saxagliptin)
Guillermin,A.L., Lloyd,A., Best,J.H., DeYoung,M.B., Samyshkin,Y.. Long-term cost-consequence analysis of exenatide once weekly vs sitagliptin or pioglitazone for the treatment of type 2 diabetes patients in the United States. Journal of Medical Economics.15 (4) (pp 654-663), 2012.	Not UK	ExQW was projected to improve health and decrease diabetes-related complication costs compared with sitagliptin or pioglitazone	Amylin (maker of exenatide)
Haalen,H.G., Pompen,M., Bergenheim,K., Mcewan,P., Townsend,R.. Cost effectiveness of adding dapagliflozin to insulin for the treatment of type 2 diabetes mellitus in the Netherlands. Clinical Drug Investigation 2014;34(2):135-46.	Comparator not in scope (dapagliflozin)	Dapagliflozin in combination with insulin was estimated to be a cost-effective treatment option for patients with T2DM whose insulin treatment regimen does not provide adequate glycaemic control in a Dutch healthcare setting	AstraZeneca (maker of dapagliflozin)
Klarenbach,S. et al. Cost-effectiveness of second-line antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin. CMAJ November, 2011 vol. 183 no. 16: E1213-E1220	Not UK	For most patients with T2DM that is inadequately controlled with metformin monotherapy, the addition of a sulphonylurea represents the most cost-effective second-line therapy	Independent

Reference	Reason for exclusion	Key finding	Sponsor
Lee,K.H., Seo,S.J., Smith-Palmer,J., Palmer,J.L., White,J.. Cost-effectiveness of switching to biphasic insulin aspart 30 from human insulin in patients with poorly controlled type 2 diabetes in South Korea. Value in Health 2009;12():Suppl-61.	Not UK	This analysis suggests that BIAsp 30 could be a cost-effective treatment option in type 2 diabetes patients poorly controlled on HI in South Korea	Novo Nordisk (maker of BIAsp 30)
Lee,W.C. & Conner,C.. Cost-effectiveness of liraglutide versus rosiglitazone, both in combination with glimepiride in treatment of type 2 diabetes in the US. Current Medical Research & Opinion 2011;27(5):897-906.	Comparator not in scope (rosiglitazone)	Compared to rosiglitazone 4 mg plus glimepiride, liraglutide (particularly at the 1.2-mg dose) plus glimepiride is a cost-effective treatment option for improving glucose control in T2DM.	Novo Nordisk (maker of liraglutide)
Lee,W.C. & Conner,C.. Results of a model analysis of the cost-effectiveness of liraglutide versus exenatide added to metformin, glimepiride, or both for the treatment of type 2 diabetes in the United States. Clinical Therapeutics 2010;32(10):1756-67.	Not UK	Liraglutide (in combination with metformin and/or glimepiride) appeared to be cost-effective in the US payer setting over a 35-year time horizon	Novo Nordisk (maker of liraglutide)
Lee,W.C., Samyshkin,Y., Langer,J.. Long-term clinical and economic outcomes associated with liraglutide versus sitagliptin therapy when added to metformin in the treatment of type 2 diabetes: a CORE Diabetes Model analysis. Journal of Medical Economics 2012;15():Suppl-37.	Not UK	The availability of liraglutide 1.2 mg and 1.8 mg with improved efficacy profiles over sitagliptin could improve patient care, with the incremental cost effectiveness ratio below $50,000 per QALY gained as add-on to metformin	Novo Nordisk (maker of liraglutide)
McEwan,P. & Evans,M.. A population model evaluating the costs and benefits associated with different oral treatment strategies in people with type 2 diabetes. Diabetes, Obesity & Metabolism 2010;12(7):623-30.	Comparator not in scope (rosiglitazone)	A treatment strategy involving the sequential addition of SU and TZD to first-line MF therapy is associated with the lowest cost and lowest gain across a population, whereas addition of TZD and SU sequentially to first-line MF therapy resulted in the highest cost and incrementally less QALY gain when compared with treatment strategies involving the addition of a DPP-4 inhibitor and SU to first-line MF (irrespective of the treatment sequence) that were associated with both less cost and greatest QALY gain	AstraZeneca, Bristol Myer Squibbs (makers of saxagliptin)
McEwan,P., Evans,M., Kan,H.. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. Diabetes, Obesity & Metabolism 2010;12(5):431-36.	Not UK	The beneficial effects of improved glycaemic control on QALYs may be offset by characteristic treatment-specific adverse effects, such as weight gain and hypoglycaemia frequency	AstraZeneca, Bristol Myer Squibbs (makers of saxagliptin)

Reference	Reason for exclusion	Key finding	Sponsor
Mezquita,Raya P., Perez,A., Ramirez de,Arellano A., Briones,T., Hunt,B.. Incretin therapy for type 2 diabetes in Spain: a cost-effectiveness analysis of liraglutide versus sitagliptin. Diabetes Therapy Research, Treatment and Education of Diabetes & Related Disorders 2013;4(2):417-30.	Not UK	Liraglutide is likely to be cost-effective versus sitagliptin from a healthcare payer perspective in Spain	Novo Nordisk (maker of liraglutide)
Minshall,M.E., Oglesby,A.K., Wintle,M.E., Valentine,W.J., Roze,S.. Estimating the long-term cost-effectiveness of exenatide in the United States: an adjunctive treatment for type 2 diabetes mellitus. Value in Health 2008;11(1):22-33.	Not UK	Exenatide used for 20 or 30 years compared with no additional treatment beyond metformin and/or a sulfonylurea is cost-effective in the adjunctive treatment of type 2 diabetes with an ICER less than $50,000 per life-year gained	Amylin, Eli Lily (makers of exenatide)
Mittendorf,T., Smith-Palmer,J., Timlin,L., Happich,M.. Evaluation of exenatide vs. insulin glargine in type 2 diabetes: cost-effectiveness analysis in the German setting. Diabetes, Obesity & Metabolism 2009;11(11):1068-79.	Not UK	Analysis of cost-effectiveness from a third-party perspective suggests that exenatide is likely to represent good value for money in the German setting	Eli Lily (maker of exenatide)
Palmer,A.J., Roze,S., Lammert,M., Valentine,W.J., Minshall,M.E., Nicklasson,L., Gall,M.A.. Comparing the long-term cost-effectiveness of repaglinide plus metformin versus nateglinide plus metformin in type 2 diabetes patients with inadequate glycaemic control: an application of the CORE Diabetes Model in type 2 diabetes. Current Medical Research & Opinion 2004;20():S51.	Not UK	Repaglinide/metformin combination was dominant to nateglinide/metformin	Novo Nordisk (maker of repaglinide)
Palmer,J.L. et al. Cost-effectiveness of switching to biphasic insulin aspart from human premix insulin in a US setting. J Med Econ. 2010;13(2):212-20	Not UK	BIAsp 30 may represent a cost-effective treatment option in the US setting for advanced type 2 diabetes patients experiencing poor glycaemic control or hypoglycaemia on human premix insulin	Novo Nordisk (maker of BIAsp 30)
Palmer,J.L., Beaudet,A., White,J., Plun-Favreau,J.. Cost-effectiveness of biphasic insulin aspart versus insulin glargine in patients with type 2 diabetes in China. Advances in Therapy 2010;27(11):814-27.	Not UK	BIAsp 30, either once- or twice-daily, improved projected life expectancy and reduced projected costs compared with IGlarg in the Chinese setting	Novo Nordisk (maker of BIAsp 30)
Palmer,J.L., Gibbs,M., Scheijbeler,H.W., Kotchie,R.W., Nielsen,S., White,J.. Cost-effectiveness of switching to biphasic insulin aspart in poorly-controlled type 2 diabetes patients in China. Advances in Therapy 2008;25(8):752-74.	Not UK	BIAsp30 would be considered cost-effective in China given a willingness-to-pay threshold of CNY 100,000 per QALY gained in type 2 diabetes patients poorly controlled on BHI	Novo Nordisk (maker of BIAsp 30)

Reference	Reason for exclusion	Key finding	Sponsor
Palmer,J.L., Goodall,G., Nielsen,S., Kotchie,R.W., Valentine,W.J., Palmer,A.J.. Cost-effectiveness of insulin aspart versus human soluble insulin in type 2 diabetes in four European countries: subgroup analyses from the PREDICTIVE study. Current Medical Research & Opinion 2008;24(5):1417-28.	Not UK	IAsp was dominant versus HI in both Sweden and Spain, would be considered cost-effective in Italy with an incremental cost-effectiveness ratio of euro 18,597 per QALY gained, but would not be considered cost-effective in Poland	Novo Nordisk (maker of IAsp)
Pinol et al. Cost-effectiveness of the addition of acarbose to the treatment of patients with type-2 diabetes in Spain. Gaceta Sanitaria.21(2) (p97-104) 2007	Not UK	The addition of acarbose to existing therapy for DM2 was associated with improvements in life expectancy and QALYs in these patients	Bayer (maker of acarbose)
Pollock,R.F. & Curtis,B.H.. A long-term analysis evaluating the cost-effectiveness of biphasic insulin lispro mix 75/25 and mix 50/50 versus long-acting basal insulin analogs in the United States. Journal of Medical Economics 2012;15(4):766-75.	Not UK	Biphasic analog insulins are likely to improve clinical outcomes and reduce costs vs LAAIs in the long-term treatment of type 2 diabetes patients in the US	Eli Lilly (maker of biphasic insulin lispro)
Pollock,R.F., Valentine,W.J., Pilgaard,T.. The cost effectiveness of rapid-acting insulin aspart compared with human insulin in type 2 diabetes patients: an analysis from the Japanese third-party payer perspective. Journal of Medical Economics 2011;14(1):36-46.	Not UK	In a Japanese type 2 diabetes population, prescribing rapid-acting insulin aspart significantly reduced cardiovascular complications over 5- and 10-year time horizons, resulting in increased quality of life and decreased costs when compared with human insulin	Novo Nordisk (maker of rapid-acting insulin aspart)
Ray,J.A., Huet,D., Valentine,W.J., Palmer,A.J., Cugnardey,N.. Long-term costs and clinical outcomes associated with metformin-glibenclamide combination tablets (Glucovance) in patients with type 2 diabetes sub-optimally controlled by metformin: A modelling study in the French setting. British Journal of Diabetes and Vascular Disease.8 (1) (pp 39-44), 2008	Not UK	From a third-party healthcare payer perspective in France, Glucovance represents a dominant treatment option versus metformin or glibenclamide for patients sub-optimally controlled on metformin monotherapy	Merck (maker of Glucovance)
Ray,J.A., Valentine,W.J., Roze,S., Nicklasson,L., Cobden,D., Raskin,P., Garber,A.. Insulin therapy in type 2 diabetes patients failing oral agents: cost-effectiveness of biphasic insulin aspart 70/30 vs. insulin glargine in the US. Diabetes, Obesity & Metabolism 2007;9(1):103-13.	Not UK	BIAsp 70/30 was projected to be cost-effective for patients with type 2 diabetes insufficiently controlled on OADs alone compared to glargine.	Novo Nordisk (maker of BIAsp 70/30)

Reference	Reason for exclusion	Key finding	Sponsor
Ridderstrale,M., Jensen,M.M., Gjesing,R.P.. Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in Denmark, Finland, Norway, and Sweden. Journal of Medical Economics.16 (4) (pp 468-478), 2013.	Not UK	The lower risk of non-severe hypoglycaemia and less weight gain associated with using insulin detemir compared with NPH insulin when initiating insulin treatment in insulin naive patients with type 2 diabetes provide economic benefits in the short-term. Based on cost/QALY threshold values, this represents good value for money in the Nordic countries.	Novo Nordisk (maker of insulin detemir)
Roze,S. et al. Acarbose in addition to existing treatments in patients with type 2 diabetes: health economic analysis in a German setting. Current Medical Research and Opinion. 2006, Vol. 22, No. 7 , Pages 1415-1424	Not UK	Addition of acarbose to existing treatment was associated with improvements in life expectancy and quality-adjusted life expectancy and provides excellent value for money over patient lifetimes in the German setting	Bayer (maker of acarbose)
Samyshkin,Y., Guillermin,A.L., Best,J.H., Brunell,S.C.. Long-term cost-utility analysis of exenatide once weekly versus insulin glargine for the treatment of type 2 diabetes patients in the US. Journal of Medical Economics 2012;15():Suppl-13.	Not UK	Treatment with EQW is projected to be cost-effective compared to treatment with IG	Amylin (maker of exenatide)
Scherbaum,W.A., Goodall,G., Erny-Albrecht,K.M., Massi-Benedetti,M., Erdmann,E.. Cost-effectiveness of pioglitazone in type 2 diabetes patients with a history of macrovascular disease: a German perspective. Cost Effectiveness & Resource Allocation 2009;7():9.	Not UK	For patients with a history of macrovascular disease, addition of pioglitazone to existing therapy reduces the long-term cumulative incidence of diabetes-complications at a cost that would be considered to represent good value for money in the German setting	Takeda (maker of pioglitazone)
Schwarz,B., Gouveia,M., Chen,J., Nocea,G., Jameson,K., Cook,J., et al. Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy. Diabetes, Obesity & Metabolism 2008;10():Suppl-55.	Not UK	Compared with adding rosiglitazone or a SU to MF, adding sitagliptin to MF is projected to be either cost saving or cost-effective for patients with type 2 diabetes who are not at HbA1c goal on MF	Merck (maker of sitagliptin)
Shearer,A.T. et al.. Lifetime health consequences and cost-effectiveness of rosiglitazone in combination with metformin for the treatment of type 2 diabetes in Spain. PharmacoEconomics November 2006, Volume 24, Issue 1 Supplement, pp 49-59	Comparator not in scope (rosiglitazone)	Rosiglitazone with metformin is a cost-effective intervention for the treatment of both overweight and obese patients with type 2 diabetes when compared with conventional care in Spain	GlaxoSmithKline (maker of rosiglitazone)

Reference	Reason for exclusion	Key finding	Sponsor
Shearer,A.T., Bagust,A., Liebl,A., Schoeffski,O.. Cost-effectiveness of rosiglitazone oral combination for the treatment of type 2 diabetes in Germany. PharmacoEconomics.24 (SUPPL.1) (pp 35-48), 2006	Comparator not in scope (rosiglitazone)	Rosiglitazone in combination with other oral agents is a cost-effective intervention for the treatment of normal weight, overweight and obese patients with type 2 diabetes when compared with conventional care in Germany.	GlaxoSmithKline (maker of rosiglitazone)
Sinha,A., Rajan,M., Hoerger,T.. Costs and consequences associated with newer medications for glycemic control in type 2 diabetes. Diabetes Care 2010;33(4):695-700.	Not UK	Exenatide and sitagliptin may confer substantial costs to health care systems. Demonstrated gains in quality and/or quantity of life are necessary for these agents to provide economic value to patients and health care systems.	Veterans Health Administration (independent)
Smith-Palmer,J., Fajardo-Montanana,C., Pollock,R.F., Ericsson,A.. Long-term cost-effectiveness of insulin detemir versus NPH insulin in type 2 diabetes in Sweden. Journal of Medical Economics 2012;15(5):977-86.	Not UK	It is likely that in the Swedish setting insulin detemir would be cost-saving in comparison with NPH insulin for the treatment of patients with type 2 diabetes	Novo Nordisk (maker of insulin detemir)
Szmurlo,D., Schubert,A., Kostrzewska,K., Rys,P.. Economic analysis of the implementation of guidelines for type 2 diabetes control developed by Diabetes Poland: What increase in costs is justified by clinical results? Polskie Archiwum Medycyny Wewnetrznej.121 (10) (pp 345-351), 2011	Not UK	Treatment according to the guidelines of Diabetes Poland may be cost-effective provided that the additional costs associated with intensification of therapy will not exceed 725 EUR per year	Novo Nordisk (maker of insulin detemir)
Teramachi,H., Ohta,H., Tachi,T., Toyoshima,M., Mizui,T., Goto,C.. Pharmacoeconomic analysis of DPP-4 inhibitors (Provisional abstract). Pharmazie 2013;68(11):909-15.	Not UK	Vildagliptin provides a superior cost-benefit	Not stated
Tilden,D.P. et al. . A lifetime modelled economic evaluation comparing pioglitazone and rosiglitazone for the treatment of type 2 diabetes mellitus in the UK. PharmacoEconomics January 2007, Volume 25, Issue 1, pp 39-54	Comparator not in scope (rosiglitazone)	In the UK, adjunctive pioglitazone may represent a cost-effective treatment choice for patients with type 2 diabetes who have insufficient glycaemic control while receiving the maximal tolerated dose of metformin monotherapy.	Takeda (maker of pioglitazone)
Tunis,S.L. & Sauriol,L.. Cost effectiveness of insulin glargine plus oral antidiabetes drugs compared with premixed insulin alone in patients with type 2 diabetes mellitus in Canada. Applied Health Economics & Health Policy 2010;8(4):267-80.	Not UK	Insulin glargine plus OADs was projected to be a cost-effective option, compared with premixed insulin only, for the treatment of insulin-naive patients with T2DM unresponsive to OADs	Sanofi (maker of insulin glargine)

Reference	Reason for exclusion	Key finding	Sponsor
Tunis,S.L., Minshall,M.E., Conner,C., McCormick,J.I., Kapor,J., Yale,J.F.. 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 & Opinion 2009;25(5):1273-84.	Not UK	Findings provide evidence for the cost-effectiveness of detemir vs. NPH in treating T1 and T2DM in Canada, and support the key role of assumptions regarding the impact of hypoglycemic events	Novo Nordisk (maker of insulin detemir)
Tunis,S.L., Minshall,M.E., St,Charles M., Pandya,B.J.. Pioglitazone versus rosiglitazone treatment in patients with type 2 diabetes and dyslipidemia: cost-effectiveness in the US. Current Medical Research & Opinion 2008;24(11):3085-96.	Comparator not in scope (rosiglitazone)	Pioglitazone (when compared to rosiglitazone) was found to have long-term value as a treatment option for T2DM patients with dyslipidemia treated within the US payer setting	Takeda (maker of pioglitazone)
Valentine,W.J., Bottomley,J.M., Palmer,A.J., Brandle,M., Foos,V., Williams,R., et al. PROactive 06: Cost-effectiveness of pioglitazone in Type 2 diabetes in the UK. Diabetic Medicine.24 (9) (pp 982-1002), 2007	Comparator not in scope (placebo)	The addition of pioglitazone to existing therapy in patients with Type 2 diabetes at high risk of further cardiovascular events is cost-effective and represents good value for money by currently accepted standards in the UK.	Takeda (maker of pioglitazone)
Valentine,W.J., Erny-Albrecht,K.M., Ray,J.A., Roze,S., Cobden,D.. Therapy conversion to insulin detemir among patients with type 2 diabetes treated with oral agents: a modeling study of cost-effectiveness in the United States. Advances in Therapy 2007;24(2):273-90.	Not UK	Therapy conversion to insulin detemir+/-OHA from OHA alone, NPH+/-OHA, or insulin glargine+/-OHA was projected to increase quality-adjusted life expectancy and to represent a cost-effective treatment option in the United States	Novo Nordisk (maker of insulin detemir)
Valentine,W.J., Goodall,G., Aagren,M., Nielsen,S., Palmer,A.J.. Evaluating the cost-effectiveness of therapy conversion to insulin detemir in patients with type 2 diabetes in Germany: a modelling study of long-term clinical and cost outcomes. Advances in Therapy 2008;25(6):567-84.	Not UK	Therapy conversion to insulin detemir +/- OADs in type 2 diabetes patients failing OADs alone, NPH or insulin glargine regimens was associated with improvements in life expectancy, quality-adjusted life expectancy and cost savings in all three scenarios evaluated	Novo Nordisk (maker of insulin detemir)
Valentine,W.J., Palmer,A.J., Lammert,M., Langer,J.. Evaluating the long-term cost-effectiveness of liraglutide versus exenatide BID in patients with type 2 diabetes who fail to improve with oral antidiabetic agents. Clinical Therapeutics 2011;33(11):1698-7112.	Not UK	Liraglutide was associated with benefits in life expectancy, QALYs, and reduced complication rates versus exenatide. Liraglutide was cost-effective from a health care payer perspective in Switzerland, Denmark, Norway, Finland, the Netherlands, and Austria	Novo Nordisk (maker of liraglutide)

Reference	Reason for exclusion	Key finding	Sponsor
Valentine,W.J., Tucker,D., Palmer,A.J., Minshall,M.E., Foos,V., Silberman,C.. Long-term cost-effectiveness of pioglitazone versus placebo in addition to existing diabetes treatment: a US analysis based on PROactive. Value in Health 2009;12(1):1-9.	Not UK	The addition of pioglitazone to existing therapy in high-risk patients with type 2 diabetes was projected to improve life expectancy, QALE and complication rates compared with placebo. Addition of pioglitazone was in the range generally considered acceptable	Takeda (maker of pioglitazone)
Valov, V. et al. Cost-effectiveness of biphasic insulin aspart 30 vs. human premix insulin in type 2 diabetes from the payer's perspective in Bulgaria. Biotechnol. & Biotechnol. Eq. 2012;26;(2):2937-2944	Not UK	Biphasic insulin aspart 30 was shown to be more effective and less costly from a third-party payer perspective than human premix insulin for type 2 diabetes in Bulgaria, and may be considered dominant.	Novo Nordisk (maker of biphasic insulin aspart 30)
Ward,A.J., Salas,M., Caro,J.J.. Health and economic impact of combining metformin with nateglinide to achieve glycemic control: Comparison of the lifetime costs of complications in the U.K. Cost Effectiveness and Resource Allocation.2 , 2004.Article Number: 2	Comparator not in scope (across therapy levels)	Although drug treatment costs are increased by combination therapy, this cost is expected to be partially offset by a reduction in the costs of treating long-term diabetes complications	Novartis (maker of nateglinide)
Watkins,J.B. & Minshall,M.E.. Application of economic analyses in U.S. managed care formulary decisions: a private payer's experience. Journal of Managed Care Pharmacy 2006;12(9):726-35.	Not UK	The P&T committee approved the drug [exenatide] for inclusion in the drug formulary based in part on the results of the pharmaco-economic model produced from the cost inputs entered into the model by the health plan pharmacists	Amylin (maker of exenatide)
Yang,L., Christensen,T., Sun,F.. Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study. Value in Health 2012;15(1:Suppl):Suppl-9.	Not UK	Conversion to IDet from an IGla regimen improved life expectancy and was a cost-saving treatment approach in a Chinese setting.	Novo Nordisk (maker of IDet)
Zhang,Y., McCoy,R.G., Mason,J.E., Smith,S.A., Shah,N.D.. Second-line agents for glycemic control for type 2 diabetes: Are newer agents better? Diabetes Care.37 (5) (pp 1338-1345), 2014	Not UK	Use of sulfonylurea as second-line therapy for type 2 diabetes generated glycemic control and QALYs comparable with those associated with other agents but at lower cost.	Independent

(a) Up to searches end June 2014
(b) Key finding was taken from the conclusion of the paper's abstract
(c) Sponsor was taken from the acknowledgements or author affiliations

Appendix F.2: Read codes used for data selection in the THIN dataset

Table 161: Read Codes Used for Selection of People With Type 2 Diabetes

Read Code	Description
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
C100100	Diabetes mellitus, adult onset, no mention of complication
C100112	Non-insulin dependent diabetes mellitus
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C104100	Diabetes mellitus, adult onset, with renal manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107400	NIDDM with peripheral circulatory disorder
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control

Read Code	Description
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer

Read Code	Description
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FQ11	Type II diabetes mellitus with exudative maculopathy
C10M.00	Lipoatrophic diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FR11	Type II diabetes mellitus with gastroparesis

Table 162: Read Codes Used To Select Risk Factor Data

Read Code	Description
1001400017	Serum cholesterol
1001400027	Haemoglobin
1001400031	High Density Lipoprotein
1003040000	Smoking
1005010100	Height
1005010200	Weight
1005010500	Blood pressure

(a) Data selected from Additional Health Data table

Table 163: Read Codes Used to Select Baseline Characteristics - Atrial Fibrilation and Peripheral Vascular Disease

Condition	Read Code	Description
Atrial Fibrillation	G573.00	Atrial fibrillation and flutter
Atrial Fibrillation	G573000	Atrial fibrillation
Atrial Fibrillation	G573200	Paroxysmal atrial fibrillation
Atrial Fibrillation	G573300	Non-rheumatic atrial fibrillation
Atrial Fibrillation	G573400	Permanent atrial fibrillation
Atrial Fibrillation	G573500	Persistent atrial fibrillation
Atrial Fibrillation	G573z00	Atrial fibrillation and flutter NOS
Peripheral Vascular Disease	G73..00	Other peripheral vascular disease
Peripheral Vascular Disease	G73..11	Peripheral ischaemic vascular disease
Peripheral Vascular Disease	G73..12	Ischaemia of legs
Peripheral Vascular Disease	G73..13	Peripheral ischaemia
Peripheral Vascular Disease	G73z.00	Peripheral vascular disease NOS
Peripheral Vascular Disease	G73z000	Intermittent claudication
Peripheral Vascular Disease	G73z011	Claudication
Peripheral Vascular Disease	G73z012	Vascular claudication
Peripheral Vascular Disease	G73zz00	Peripheral vascular disease NOS
Peripheral Vascular Disease	Gyu7400	[X]Other specified peripheral vascular diseases
Peripheral Vascular Disease	G734.00	Peripheral arterial disease
Peripheral Vascular Disease	G73y.00	Other specified peripheral vascular disease

Table 164: Read Codes Used to Select Pre-Existing Complications

Complication	Read Code	Description
Amputation	14N4100	H/O: lower limb amputation
Amputation	2G4A.00	O/E - amputated left midfoot
Amputation	2G4B.00	O/E - amputated right midfoot
Amputation	7L06211	Kirk amputation of leg through thigh
Amputation	7L06411	Boyd amputation of leg below knee
Amputation	7L06412	Burgess amputation of leg below knee
Amputation	7L06413	Guyon amputation of leg below knee
Amputation	7L06y00	Other specified amputation of leg
Amputation	7L07011	Pirogoff amputation of foot through ankle
Amputation	7L07012	Syme amputation of foot through ankle
Amputation	7L07111	Boyd amputation of hindfoot
Amputation	7L07211	Lisfranc tarsometatarsal amputation
Amputation	7L07212	Tarsometatarsal amputation
Amputation	7L07311	Chopart midtarsal amputation
Amputation	7L07312	Ray transmetatarsal amputation
Amputation	7L07y00	Other specified amputation of foot
Amputation	7L07z11	Hey amputation of foot
Amputation	7L08y00	Other specified amputation of toe
Amputation	2G42.00	O/E - Amputated right leg
Amputation	2G43.00	O/E - Amputated left leg
Amputation	2G44.00	O/E - Amputated right above knee
Amputation	2G45.00	O/E - Amputated left above knee
Amputation	2G46.00	O/E - Amputated right below knee
Amputation	2G47.00	O/E - Amputated left below knee
Amputation	2G56.00	O/E - Amputated right forefoot
Amputation	2G57.00	O/E - Amputated left forefoot
Amputation	2G61.00	O/E - Amputated right toe
Amputation	2G62.00	O/E - Amputated left toe
Amputation	7L06.00	Amputation of leg
Amputation	7L06200	Amputation above knee
Amputation	7L06212	Amputation of leg through thigh
Amputation	7L06300	Amputation through knee
Amputation	7L06400	Amputation below knee
Amputation	7L06z00	Amputation of leg NOS
Amputation	7L07.00	Amputation of foot
Amputation	7L07000	Amputation through ankle
Amputation	7L07300	Amputation through metatarsal bones
Amputation	7L07z00	Amputation of foot NOS
Amputation	7L08.00	Amputation of toe
Amputation	7L08000	Amputation hallux
Amputation	7L08011	Amputation great toe
Amputation	7L08100	Amputation of phalanx of toe
Amputation	7L08300	Amputation lesser toe
Amputation	7L08z00	Amputation of toe NOS

Complication	Read Code	Description
Blindness	F490.00	Blindness, both eyes
Blindness	F490000	Unspecified blindness both eyes
Blindness	F490100	Both eyes total visual impairment
Blindness	F490200	Better eye: near total VI, Lesser eye: unspecified
Blindness	F490300	Better eye: near total VI, Lesser eye: total VI
Blindness	F490400	Better eye: near total VI, Lesser eye: near total VI
Blindness	F490500	Better eye: profound VI, Lesser eye: unspecified
Blindness	F490600	Better eye: profound VI, Lesser eye: total VI
Blindness	F490700	Better eye: profound VI, Lesser eye: near total VI
Blindness	F490800	Better eye: profound VI, Lesser eye: profound VI
Blindness	F490900	Acquired blindness, both eyes
Blindness	F490z00	Blindness both eyes NOS
Blindness	F491.00	Better eye: low vision, Lesser eye: profound VI
Blindness	F491000	One eye blind, one eye low vision
Blindness	F491100	Better eye: severe VI, Lesser eye: blind, unspecified
Blindness	F491200	Better eye: severe VI, Lesser eye: total VI
Blindness	F491300	Better eye: severe VI, Lesser eye: near total VI
Blindness	F491400	Better eye: severe VI, Lesser eye: profound VI
Blindness	F491500	Better eye: moderate VI, Lesser eye: blind, unspecified
Blindness	F491600	Better eye: moderate VI, Lesser eye: total VI
Blindness	F491700	Better eye: moderate VI, Lesser eye: near total VI
Blindness	F491800	Better eye: moderate VI, Lesser eye: profound VI
Blindness	F491z00	One eye blind, one eye low vision NOS
Blindness	F497.00	Severe visual impairment, binocular
Blindness	F492.00	Low vision, both eyes
Blindness	F492000	Low vision, both eyes unspecified
Blindness	F492100	Better eye: severe VI, Lesser eye: low vision unspecified
Blindness	F492200	Better eye: severe VI, Lesser eye: severe VI
Blindness	F492300	Better eye: moderate VI, Lesser eye: low vision unspecified
Blindness	F492400	Better eye: moderate VI, Lesser eye: severe VI
Blindness	F492500	Better eye: moderate VI, Lesser eye: moderate VI
Blindness	F492z00	Low vision, both eyes NOS
Blindness	F498.00	Moderate visual impairment, binocular
Blindness	6689.00	Registered blind
Blindness	6689.11	Registered severely sight impaired
Blindness	F493.00	Visual loss, both eyes unqualified
Blindness	668D.00	Registered sight impaired
Blindness	F499.00	Mild or no visual impairment, binocular
Blindness	2B69.00	O/E -R-eye counts fingers only
Blindness	2B6A.00	O/E-R-eye perceives light only
Blindness	2B6A.11	O/E - blind R-eye
Blindness	2B6B.00	O/E - R-eye completely blind
Blindness	2B79.00	O/E -L-eye counts fingers only
Blindness	2B7A.00	O/E-L-eye perceives light only
Blindness	2B7A.11	O/E - blind L-eye

Complication	Read Code	Description
Blindness	2B7B.00	O/E - L-eye completely blind
Blindness	22EF.00	O/E - has one eye
Blindness	2B6C.00	O/E - R-eye sees hand movements
Blindness	2B7C.00	O/E - L-eye sees hand movements
Blindness	F495.00	Profound impairment, one eye
Blindness	F495000	Blindness, one eye, unspecified
Blindness	F495100	Lesser eye: total visual impairment, Better eye: unspecified
Blindness	F495200	Lesser eye: total VI, Better eye: near normal vision
Blindness	F495300	Lesser eye: total VI, Better eye: normal vision
Blindness	F495400	Lesser eye: near total VI, Better eye: unspecified
Blindness	F495500	Lesser eye: near total VI, Better eye: near normal vision
Blindness	F495600	Lesser eye: near total VI, Better eye: normal vision
Blindness	F495700	Lesser eye: profound VI, Better eye: unspecified
Blindness	F495800	Lesser eye: profound VI, Better eye: near normal vision
Blindness	F495900	Lesser eye: profound VI, Better eye: normal vision
Blindness	F495A00	Acquired blindness, one eye
Blindness	F495z00	Profound impairment one eye NOS
Blindness	2B7E.00	O/E - visual acuity L-eye=3/60
Blindness	2B6E.00	O/E - visual acuity R-eye=3/60
Blindness	2B6P.00	O/E - pinhole R-eye sees hand movements
Blindness	2B6Q.00	O/E - pinhole R-eye counts fingers only
Blindness	2B6R.00	O/E - pinhole R-eye perceives light only
Blindness	2B6S.00	O/E - pinhole R-eye completely blind
Blindness	2B7P.00	O/E - pinhole L-eye sees hand movements
Blindness	2B7Q.00	O/E - pinhole L-eye counts fingers only
Blindness	2B7R.00	O/E - pinhole L-eye perceives light only
Blindness	2B7S.00	O/E - pinhole L-eye completely blind
Blindness	F49A.00	Blindness, monocular
Blindness	2B65.00	O/E - visual acuity R-eye=6/18
Blindness	2B66.00	O/E - visual acuity R-eye=6/24
Blindness	2B67.00	O/E - visual acuity R-eye=6/36
Blindness	2B68.00	O/E - visual acuity R-eye=6/60
Blindness	2B75.00	O/E - visual acuity L-eye=6/18
Blindness	2B76.00	O/E - visual acuity L-eye=6/24
Blindness	2B77.00	O/E - visual acuity L-eye=6/36
Blindness	2B78.00	O/E - visual acuity L-eye=6/60
Blindness	F496.00	Low vision, one eye
Blindness	F496000	Low vision, one eye, unspecified
Blindness	F496100	Lesser eye: severe VI, Better eye: unspecified
Blindness	F496200	Lesser eye: severe VI, Better eye: near normal vision
Blindness	F496300	Lesser eye: severe VI, Better eye: normal vision
Blindness	F496400	Lesser eye: moderate VI, Better eye: unspecified
Blindness	F496500	Lesser eye: moderate VI, Better eye: near normal vision
Blindness	F496600	Lesser eye: moderate VI, Better eye: normal vision
Blindness	F496z00	Low vision, one eye NOS

Complication	Read Code	Description
Blindness	2B6f.00	O/E visual acuity right eye = 6/20
Blindness	2B7f.00	O/E - visual acuity left eye = 6/20
Blindness	F49B.00	Severe visual impairment, monocular
Blindness	F49y.00	Visual loss, one eye, unqualified
Blindness	F49C.00	Moderate visual impairment, monocular
Blindness	1056350000	Visual Acuity Left Eye (additional codes)
Blindness	1056300000	Visual Acuity Right Eye (additional codes)
Congestive Heart Failure	388D.00	NYHA classif heart fail symps
Congestive Heart Failure	G58..00	Heart failure
Congestive Heart Failure	G58..11	Cardiac failure
Congestive Heart Failure	G580.00	Congestive heart failure
Congestive Heart Failure	G580.11	Congestive cardiac failure
Congestive Heart Failure	G580.12	Right heart failure
Congestive Heart Failure	G580.13	Right ventricular failure
Congestive Heart Failure	G580.14	Biventricular failure
Congestive Heart Failure	G580000	Acute congestive heart failure
Congestive Heart Failure	G580100	Chroncongestive heart failure
Congestive Heart Failure	G580200	Decompensated cardiac failure
Congestive Heart Failure	G580300	Compensated cardiac failure
Congestive Heart Failure	G581.00	Left ventricular failure
Congestive Heart Failure	G581.11	Asthma - cardiac
Congestive Heart Failure	G581.12	Pulmonary oedema - acute
Congestive Heart Failure	G581.13	Impaired left ventricular function
Congestive Heart Failure	G581000	Acute left ventricular failure
Congestive Heart Failure	G582.00	Acute heart failure
Congestive Heart Failure	G58z.00	Heart failure NOS
Congestive Heart Failure	G58z.11	Weak heart
Congestive Heart Failure	G58z.12	Cardiac failure NOS
Congestive Heart Failure	1O1..00	Heart failure confirmed
Congestive Heart Failure	SP11100	Cardiac insuffic.comp.of care
Congestive Heart Failure	SP11111	Heart failure as a complication of care
Congestive Heart Failure	585f.00	Echocardiogram shows LVSDF
Congestive Heart Failure	585g.00	Echocardiogram shows LVDDF
Congestive Heart Failure	G583.00	Heart failure norm eject frac
Congestive Heart Failure	G583.11	HFNEF - heart failure with normal ejection fraction
Congestive Heart Failure	G583.12	Heart failure with preserved ejection fraction
Congestive Heart Failure	G584.00	Right ventricular failure
Congestive Heart Failure	G5yyC00	Diastolic dysfunction
Congestive Heart Failure	388D.00	NYHA classif heart fail symps
Congestive Heart Failure	G58..00	Heart failure
Congestive Heart Failure	G58..11	Cardiac failure
Congestive Heart Failure	G580.00	Congestive heart failure
Congestive Heart Failure	G580.11	Congestive cardiac failure
Congestive Heart Failure	G580.12	Right heart failure
Congestive Heart Failure	G580.13	Right ventricular failure
Congestive Heart Failure	G580.14	Biventricular failure

Complication	Read Code	Description
Congestive Heart Failure	G580000	Acute congestive heart failure
Congestive Heart Failure	G580100	Chroncongestive heart failure
Congestive Heart Failure	G580200	Decompensated cardiac failure
Congestive Heart Failure	G580300	Compensated cardiac failure
Congestive Heart Failure	G581.00	Left ventricular failure
Congestive Heart Failure	G581.11	Asthma - cardiac
Congestive Heart Failure	G581.12	Pulmonary oedema - acute
Congestive Heart Failure	G581.13	Impaired left ventricular function
Congestive Heart Failure	G581000	Acute left ventricular failure
Congestive Heart Failure	G582.00	Acute heart failure
Congestive Heart Failure	G58z.00	Heart failure NOS
Congestive Heart Failure	G58z.11	Weak heart
Congestive Heart Failure	G58z.12	Cardiac failure NOS
Congestive Heart Failure	1O1..00	Heart failure confirmed
Congestive Heart Failure	SP11100	Cardiac insuffic.comp.of care
Congestive Heart Failure	SP11111	Heart failure as a complication of care
Congestive Heart Failure	585f.00	Echocardiogram shows LVSDF
Congestive Heart Failure	585g.00	Echocardiogram shows LVDDF
Congestive Heart Failure	G583.00	Heart failure norm eject frac
Congestive Heart Failure	G583.11	HFNEF - heart failure with normal ejection fraction
Congestive Heart Failure	G583.12	Heart failure with preserved ejection fraction
Congestive Heart Failure	G584.00	Right ventricular failure
Congestive Heart Failure	G5yyC00	Diastolic dysfunction
Ischaemic Heart Disease	G3...00	Ischaemic heart disease
Ischaemic Heart Disease	G31..00	Other acute and subacute ischaemic heart disease
Ischaemic Heart Disease	G310.00	Postmyocardial infarction syndrome
Ischaemic Heart Disease	G311.00	Preinfarction syndrome
Ischaemic Heart Disease	G311000	Myocardial infarction aborted
Ischaemic Heart Disease	G311100	Unstable angina
Ischaemic Heart Disease	G311200	Angina at rest
Ischaemic Heart Disease	G311300	Refractory angina
Ischaemic Heart Disease	G311400	Worsening angina
Ischaemic Heart Disease	G311500	Acute coronary syndrome
Ischaemic Heart Disease	G311z00	Preinfarction syndrome NOS
Ischaemic Heart Disease	G312.00	Coronary thrombosis not resulting in myocardial infarction
Ischaemic Heart Disease	G31y.00	Other acute and subacute ischaemic heart disease
Ischaemic Heart Disease	G31y000	Acute coronary insufficiency
Ischaemic Heart Disease	G31y100	Microinfarction of heart
Ischaemic Heart Disease	G31y200	Subendocardial ischaemia
Ischaemic Heart Disease	G31y300	Transient myocardial ischaemia
Ischaemic Heart Disease	G31yz00	Other acute and subacute ischaemic heart disease NOS
Ischaemic Heart Disease	G32..00	Old myocardial infarction
Ischaemic Heart Disease	G33..00	Angina pectoris
Ischaemic Heart Disease	G330.00	Angina decubitus
Ischaemic Heart Disease	G330000	Nocturnal angina

Complication	Read Code	Description
Ischaemic Heart Disease	G330z00	Angina decubitus NOS
Ischaemic Heart Disease	G33z.00	Angina pectoris NOS
Ischaemic Heart Disease	G33z000	Status anginosus
Ischaemic Heart Disease	G33z100	Stenocardia
Ischaemic Heart Disease	G33z200	Syncope anginosa
Ischaemic Heart Disease	G33z300	Angina on effort
Ischaemic Heart Disease	G33z400	Ischaemic chest pain
Ischaemic Heart Disease	G33z500	Post infarct angina
Ischaemic Heart Disease	G33z600	New onset angina
Ischaemic Heart Disease	G33z700	Stable angina
Ischaemic Heart Disease	G33zz00	Angina pectoris NOS
Ischaemic Heart Disease	G34..00	Other chronic ischaemic heart disease
Ischaemic Heart Disease	G340.00	Coronary atherosclerosis
Ischaemic Heart Disease	G340000	Single coronary vessel disease
Ischaemic Heart Disease	G340100	Double coronary vessel disease
Ischaemic Heart Disease	G342.00	Atherosclerotic cardiovascular disease
Ischaemic Heart Disease	G343.00	Ischaemic cardiomyopathy
Ischaemic Heart Disease	G344.00	Silent myocardial ischaemia
Ischaemic Heart Disease	G34y.00	Other specified chronic ischaemic heart disease
Ischaemic Heart Disease	G34y000	Chronic coronary insufficiency
Ischaemic Heart Disease	G34y100	Chronic myocardial ischaemia
Ischaemic Heart Disease	G34yz00	Other specified chronic ischaemic heart disease NOS
Ischaemic Heart Disease	G34z.00	Other chronic ischaemic heart disease NOS
Ischaemic Heart Disease	G34z000	Asymptomatic coronary heart disease
Ischaemic Heart Disease	G35..00	Subsequent myocardial infarction
Ischaemic Heart Disease	G350.00	Subsequent myocardial infarction of anterior wall
Ischaemic Heart Disease	G351.00	Subsequent myocardial infarction of inferior wall
Ischaemic Heart Disease	G353.00	Subsequent myocardial infarction of other sites
Ischaemic Heart Disease	G35X.00	Subsequent myocardial infarction of unspecified site
Ischaemic Heart Disease	G36..00	Certain current complication follow acute myocardial infarct
Ischaemic Heart Disease	G360.00	Haemopericardium/current comp folow acut myocard infarct
Ischaemic Heart Disease	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
Ischaemic Heart Disease	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
Ischaemic Heart Disease	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Ischaemic Heart Disease	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Ischaemic Heart Disease	G39..00	Coronary microvascular disease
Ischaemic Heart Disease	G3y..00	Other specified ischaemic heart disease
Ischaemic Heart Disease	G3z..00	Ischaemic heart disease NOS
Ischaemic Heart Disease	Gyu3.00	[X]Ischaemic heart diseases
Ischaemic Heart Disease	Gyu3000	[X]Other forms of angina pectoris
Ischaemic Heart Disease	Gyu3100	[X]Other current complicatns following acute myocard infarct
Ischaemic Heart Disease	Gyu3200	[X]Other forms of acute ischaemic heart disease
Ischaemic Heart Disease	Gyu3300	[X]Other forms of chronic ischaemic heart disease

Complication	Read Code	Description
Ischaemic Heart Disease	Gyu3500	[X]Subsequent myocardial infarction of other sites
Ischaemic Heart Disease	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Ischaemic Heart Disease	G3...00	Ischaemic heart disease
Ischaemic Heart Disease	G31..00	Other acute and subacute ischaemic heart disease
Ischaemic Heart Disease	G310.00	Postmyocardial infarction syndrome
Ischaemic Heart Disease	G311.00	Preinfarction syndrome
Ischaemic Heart Disease	G311000	Myocardial infarction aborted
Ischaemic Heart Disease	G311100	Unstable angina
Ischaemic Heart Disease	G311200	Angina at rest
Ischaemic Heart Disease	G311300	Refractory angina
Ischaemic Heart Disease	G311400	Worsening angina
Ischaemic Heart Disease	G311500	Acute coronary syndrome
Ischaemic Heart Disease	G311z00	Preinfarction syndrome NOS
Ischaemic Heart Disease	G312.00	Coronary thrombosis not resulting in myocardial infarction
Ischaemic Heart Disease	G31y.00	Other acute and subacute ischaemic heart disease
Ischaemic Heart Disease	G31y000	Acute coronary insufficiency
Ischaemic Heart Disease	G31y100	Microinfarction of heart
Ischaemic Heart Disease	G31y200	Subendocardial ischaemia
Ischaemic Heart Disease	G31y300	Transient myocardial ischaemia
Ischaemic Heart Disease	G31yz00	Other acute and subacute ischaemic heart disease NOS
Ischaemic Heart Disease	G32..00	Old myocardial infarction
Ischaemic Heart Disease	G33..00	Angina pectoris
Ischaemic Heart Disease	G330.00	Angina decubitus
Ischaemic Heart Disease	G330000	Nocturnal angina
Ischaemic Heart Disease	G330z00	Angina decubitus NOS
Ischaemic Heart Disease	G33z.00	Angina pectoris NOS
Ischaemic Heart Disease	G33z000	Status anginosus
Ischaemic Heart Disease	G33z100	Stenocardia
Ischaemic Heart Disease	G33z200	Syncope anginosa
Ischaemic Heart Disease	G33z300	Angina on effort
Ischaemic Heart Disease	G33z400	Ischaemic chest pain
Ischaemic Heart Disease	G33z500	Post infarct angina
Ischaemic Heart Disease	G33z600	New onset angina
Ischaemic Heart Disease	G33z700	Stable angina
Ischaemic Heart Disease	G33zz00	Angina pectoris NOS
Ischaemic Heart Disease	G34..00	Other chronic ischaemic heart disease
Ischaemic Heart Disease	G340.00	Coronary atherosclerosis
Ischaemic Heart Disease	G340000	Single coronary vessel disease
Ischaemic Heart Disease	G340100	Double coronary vessel disease
Ischaemic Heart Disease	G342.00	Atherosclerotic cardiovascular disease
Ischaemic Heart Disease	G343.00	Ischaemic cardiomyopathy
Ischaemic Heart Disease	G344.00	Silent myocardial ischaemia
Ischaemic Heart Disease	G34y.00	Other specified chronic ischaemic heart disease
Ischaemic Heart Disease	G34y000	Chronic coronary insufficiency
Ischaemic Heart Disease	G34y100	Chronic myocardial ischaemia

Complication	Read Code	Description
Ischaemic Heart Disease	G34yz00	Other specified chronic ischaemic heart disease NOS
Ischaemic Heart Disease	G34z.00	Other chronic ischaemic heart disease NOS
Ischaemic Heart Disease	G34z000	Asymptomatic coronary heart disease
Ischaemic Heart Disease	G35..00	Subsequent myocardial infarction
Ischaemic Heart Disease	G350.00	Subsequent myocardial infarction of anterior wall
Ischaemic Heart Disease	G351.00	Subsequent myocardial infarction of inferior wall
Ischaemic Heart Disease	G353.00	Subsequent myocardial infarction of other sites
Ischaemic Heart Disease	G35X.00	Subsequent myocardial infarction of unspecified site
Ischaemic Heart Disease	G36..00	Certain current complication follow acute myocardial infarct
Ischaemic Heart Disease	G360.00	Haemopericardium/current comp folow acut myocard infarct
Ischaemic Heart Disease	G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
Ischaemic Heart Disease	G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
Ischaemic Heart Disease	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Ischaemic Heart Disease	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Ischaemic Heart Disease	G39..00	Coronary microvascular disease
Ischaemic Heart Disease	G3y..00	Other specified ischaemic heart disease
Ischaemic Heart Disease	G3z..00	Ischaemic heart disease NOS
Ischaemic Heart Disease	Gyu3.00	[X]Ischaemic heart diseases
Ischaemic Heart Disease	Gyu3000	[X]Other forms of angina pectoris
Ischaemic Heart Disease	Gyu3100	[X]Other current complicatns following acute myocard infarct
Ischaemic Heart Disease	Gyu3200	[X]Other forms of acute ischaemic heart disease
Ischaemic Heart Disease	Gyu3300	[X]Other forms of chronic ischaemic heart disease
Ischaemic Heart Disease	Gyu3500	[X]Subsequent myocardial infarction of other sites
Ischaemic Heart Disease	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Ischaemic Heart Disease	G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
Ischaemic Heart Disease	G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
Ischaemic Heart Disease	G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
Ischaemic Heart Disease	G39..00	Coronary microvascular disease
Ischaemic Heart Disease	G3y..00	Other specified ischaemic heart disease
Ischaemic Heart Disease	G3z..00	Ischaemic heart disease NOS
Ischaemic Heart Disease	Gyu3.00	[X]Ischaemic heart diseases
Ischaemic Heart Disease	Gyu3000	[X]Other forms of angina pectoris
Ischaemic Heart Disease	Gyu3100	[X]Other current complicatns following acute myocard infarct
Ischaemic Heart Disease	Gyu3200	[X]Other forms of acute ischaemic heart disease
Ischaemic Heart Disease	Gyu3300	[X]Other forms of chronic ischaemic heart disease
Ischaemic Heart Disease	Gyu3500	[X]Subsequent myocardial infarction of other sites
Ischaemic Heart Disease	Gyu3600	[X]Subsequent myocardial infarction of unspecified site
Myocardial Infarction	G380.00	Postoperative transmural myocardial infarction anterior wall
Myocardial Infarction	G301z00	Anterior myocardial infarction NOS
Myocardial Infarction	G301100	Acute anteroseptal infarction
Myocardial Infarction	G301000	Acute anteroapical infarction

Complication	Read Code	Description
Myocardial Infarction	G301.00	Other specified anterior myocardial infarction
Myocardial Infarction	G300.00	Acute anterolateral infarction
Myocardial Infarction	3233.00	ECG: antero-septal infarct.
Myocardial Infarction	G381.00	Postoperative transmural myocardial infarction inferior wall
Myocardial Infarction	G30yz00	Other acute myocardial infarction NOS
Myocardial Infarction	G308.00	Inferior myocardial infarction NOS
Myocardial Infarction	G303.00	Acute inferoposterior infarction
Myocardial Infarction	G302.00	Acute inferolateral infarction
Myocardial Infarction	G30B.00	Acute posterolateral myocardial infarction
Myocardial Infarction	G382.00	Postoperative transmural myocardial infarction other sites
Myocardial Infarction	G30y200	Acute septal infarction
Myocardial Infarction	G306.00	True posterior myocardial infarction
Myocardial Infarction	G305.00	Lateral myocardial infarction NOS
Myocardial Infarction	G304.00	Posterior myocardial infarction NOS
Myocardial Infarction	3236.00	ECG: lateral infarction
Myocardial Infarction	3234.00	ECG:posterior/inferior infarct
Myocardial Infarction	Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Myocardial Infarction	G383.00	Postoperative transmural myocardial infarction unspec site
Myocardial Infarction	G30X000	Acute ST segment elevation myocardial infarction
Myocardial Infarction	G30X.00	Acute transmural myocardial infarction of unspecif site
Myocardial Infarction	G309.00	Acute Q-wave infarct
Myocardial Infarction	G384.00	Postoperative subendocardial myocardial infarction
Myocardial Infarction	G30y100	Acute papillary muscle infarction
Myocardial Infarction	G307100	Acute non-ST segment elevation myocardial infarction
Myocardial Infarction	G307000	Acute non-Q wave infarction
Myocardial Infarction	G307.00	Acute subendocardial infarction
Myocardial Infarction	3235.00	ECG: subendocardial infarct
Myocardial Infarction	G38z.00	Postoperative myocardial infarction, unspecified
Myocardial Infarction	G38..00	Postoperative myocardial infarction
Myocardial Infarction	G30z.00	Acute myocardial infarction NOS
Myocardial Infarction	G30y000	Acute atrial infarction
Myocardial Infarction	G30y.00	Other acute myocardial infarction
Myocardial Infarction	G30A.00	Mural thrombosis
Myocardial Infarction	G30..00	Acute myocardial infarction
Myocardial Infarction	323Z.00	ECG: myocardial infarct NOS
Myocardial Infarction	323..00	ECG: myocardial infarction
Myocardial Infarction	R21..00	[D]Sudden death, cause unknown
Myocardial Infarction	R211.00	[D]Instantaneous death
Myocardial Infarction	R212.00	[D]Death less than 24 hours from onset of illness
Myocardial Infarction	R212000	[D]Death, not instantaneous cause unknown
Myocardial Infarction	R212100	[D]Died, with no sign of disease
Myocardial Infarction	R212z00	[D]Death less than 24 hours from onset of illness NOS
Myocardial Infarction	R21z.00	[D]Sudden death, cause unknown NOS
Renal Failure	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
Renal Failure	1Z14.00	Chronic kidney disease stage 5

Complication	Read Code	Description
Renal Failure	Kyu2100	[X]Other chronic renal failure
Renal Failure	K0D..00	End-stage renal disease
Renal Failure	K05..00	Chronic renal failure
Renal Failure	K06..00	Renal failure unspecified
Renal Failure	Kyu2.00	[X]Renal failure
Renal Failure	1Z1K.00	Chronic kidney disease stage 5 with proteinuria
Stroke	C13A.00	Pituitary apoplexy
Stroke	F11x200	Cerebral degeneration due to cerebrovascular disease
Stroke	G6...00	Cerebrovascular disease
Stroke	G61..00	Intracerebral haemorrhage
Stroke	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
Stroke	G61..12	Stroke due to intracerebral haemorrhage
Stroke	G610.00	Cortical haemorrhage
Stroke	G611.00	Internal capsule haemorrhage
Stroke	G612.00	Basal nucleus haemorrhage
Stroke	G613.00	Cerebellar haemorrhage
Stroke	G614.00	Pontine haemorrhage
Stroke	G615.00	Bulbar haemorrhage
Stroke	G616.00	External capsule haemorrhage
Stroke	G617.00	Intracerebral haemorrhage, intraventricular
Stroke	G618.00	Intracerebral haemorrhage, multiple localized
Stroke	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
Stroke	G61X000	Left sided intracerebral haemorrhage, unspecified
Stroke	G61X100	Right sided intracerebral haemorrhage, unspecified
Stroke	G61z.00	Intracerebral haemorrhage NOS
Stroke	G63y000	Cerebral infarct due to thrombosis of precerebral arteries
Stroke	G63y100	Cerebral infarction due to embolism of precerebral arteries
Stroke	G640000	Cerebral infarction due to thrombosis of cerebral arteries
Stroke	G641000	Cerebral infarction due to embolism of cerebral arteries
Stroke	G64z.00	Cerebral infarction NOS
Stroke	G64z.11	Brainstem infarction NOS
Stroke	G64z.12	Cerebellar infarction
Stroke	G64z000	Brainstem infarction
Stroke	G64z200	Left sided cerebral infarction
Stroke	G64z300	Right sided cerebral infarction
Stroke	G64z400	Infarction of basal ganglia
Stroke	G65z100	Intermittent cerebral ischaemia
Stroke	G66..00	Stroke and cerebrovascular accident unspecified
Stroke	G663.00	Brain stem stroke syndrome
Stroke	G664.00	Cerebellar stroke syndrome
Stroke	G667.00	Left sided CVA
Stroke	G668.00	Right sided CVA
Stroke	G669.00	Cerebral palsy, not congenital or infantile, acute
Stroke	G671z00	Generalised ischaemic cerebrovascular disease NOS
Stroke	G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries

Complication	Read Code	Description
Stroke	G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Stroke	G6z..00	Cerebrovascular disease NOS
Stroke	Gyu6200	[X]Other intracerebral haemorrhage
Stroke	Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Stroke	Gyu6400	[X]Other cerebral infarction
Stroke	Gyu6800	[X]Cerebral arteritis in infectious and parasitic diseases
Stroke	Gyu6900	[X]Cerebral arteritis in other diseases CE
Stroke	Gyu6A00	[X]Other cerebrovascular disorders in diseases CE
Stroke	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Stroke	Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries

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