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HQT Diagnostics	FULL	General	General	Test for Fatty Acids and supplement to achieve: • **Omega-3 Index: >8%** • **Omega-6/3 Ratio: <3:1** This is being used widely in Germany by clients of HQT Diagnostics to treat both Type1 and Type2 Diabetes More at: www.hqt-diagnostics.com www.sanomega.de	Thank you. This topic is not in the scope. This matter has been referred to the NICE guideline surveillance team.
HQT Diagnostics	FULL	General	General	Omega-3 Poly Unsaturated Fatty Acids (PUFA) are involved in glucose level control, insulin sensitivity and prevention of heart disease More at: www.expertomega3.com/omega-3-study.asp?id=2 http://jama.jamanetwork.com/article.aspx?articleid=2088851	Thank you. This topic is not in the scope. This matter has been referred to the NICE guideline surveillance team

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HQT Diagnostics	FULL	General	General	Vitamin D - with co-factors such as Calcium and Magnesium – appears to both prevent and treat Diabetes General Practitioners should test and supplement 25(OH)D to between 100-150 nmol/L for all Diabetes patients and review blood tests after 3 months GPs should also test levels of Magnesium and Calcium More at: www.vitamindwiki.com/Overview+Diabetes+and+vitamin+D	Thank you. This topic is not in the scope. This matter has been referred to the NICE guideline surveillance team
HQT Diagnostics	FULL	General	General	Vitamin D 25(OH)D should be supplemented to between 100-150 nmol/L This should reduce fatty deposition in the liver and also improve vascular reactivity. More at: http://www.eurekaselect.com/72897/article	Thank you. This topic is not in the scope. This matter has been referred to the NICE guideline surveillance team

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HQT Diagnostics	FULL	General	General	Refer patient to Dietitian or Nutritional Therapist for advice about Diet & Lifestyle and possible trial of a Ketogenic Diet More at: http://www.ijcasereportsandimages.com/archive/2014/010-2014-ijcri/CR-10435-10-2014-clemens/ijcri-1043510201435-toth.pdf	Thank you. This topic is not in the scope. This matter has been referred to the NICE guideline surveillance team
Association of British Clinical Diabetologists	FULL	General	General	There is no mention of prevention of Type 1. There have been several studies published regarding primary prevention with Vitamin D in at risk Scandinavian children, showing a positive result and cows milk protein (underway) and early insulin therapy (no effect). No recommendations are currently being made, although Vitamin D supplements in pregnancy appears to be recommended in general. Studies in immunomodulatory therapy have short lived effects and many side effects. Anti CD3 trials are ongoing.	Thank you for your comment. We agree that prevention is an important issue but it is not in the scope for this guideline. This matter has been referred to the NICE guideline surveillance team
Welsh Endocrine and	FULL	General	General	This is a welcome update to the previous guideline. The recommendations are largely not controversial and	Thank you for your comment. We have added a further recommendation: "Use other basal

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Diabetes Society				consistent with clinical practice. There is a welcome emphasis on supporting self-management. It would be beneficial to have a recommendation on the use of insulin degludec in type1 diabetes.	insulin regimens only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the preferences of the adult with type 1 diabetes and acquisition cost. [new 2015]
Association of British Healthcare Industries	FULL	General	General	There are four key points that ABHI wish to make as regards the Diabetes consultations. 1. Issue identification 2. Collation, interpretation and grading of evidence 3. Intervention Level Assessment 4. Acquisition cost v value approach **Issue identification** The draft guidelines do not make reference to the issue(s) to be addressed. We would welcome an explicit reference to current levels of adoption and reinforcement of the gap that the guidelines will address **Collation, interpretation and grading of evidence**	Thank you for your comments. 1. Issues to be addressed are set out in the guideline scope 2. Our methodology considered all these factors, by critical review of the data we analysed. The methodology used in the guideline is highly robust and reflects that of both Cochrane and GRADE methodology (including the issues of blinding). We conduct critical reviews of the evidence and consider all of

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				Evidence appears to have been judged using a methodology more appropriate for pharmaceuticals that does not account for differences in research methodologies for medical devices, thereby, leading to certain evidenced being judged as weak. For example, studies that were not blinded have been appraised as week even though this approach is neither practically possible or reflect the real word self injection experience. When assessing medical devices, NICE need to take into account differences with pharmaceuticals and therefore the interpretation and collection of evidence. Additionally NICE should ensure inclusion of the most recent evidence given that literature searches' are time defined and may leave any published guidance slightly off pace with the most recent clinical evidence. **Intervention Level Assessment** We recommend that NICE should take a holistic view when developing guidelines to ensure that assessment is made at an interventional level rather than explicit statement on individual products or product categories; there are other more appropriate routes where these	the factors that you mention, and so we are glad that you agree with our methodology. With regards to blinding, even though it may not be possible for a study to be blinded, the fact that there may have been lack of blinding (patients or outcome assessors) can still lead to /introduce bias, and so the evidence has been appropriately downgraded for being at 'risk' of bias. In response to your comment about including the most recent evidence. Our literature searches are rerun 8 weeks before the guideline goes out for consultation, and so recently published study data is captured and is included where it meets the

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				issues can be addressed, such as via Medical Technology Evaluation Programme. Equally it should be ensured that all relevant educational, training and supply chain issues are incorporated **Acquisition cost versus value approach** The guidance indicates that "if possible" the lowest acquisition cost needle should be used. While the full guidance may put that in to context the presentation of this guidance could erroneously lead to the acquisition cost being the most important factor in the selection of needles. This is not in the best interest of patients and could impact on their ability to control their diabetes. An assumption of commodity status is not founded, with the guideline development group recognising that needle type can have an influence on outcomes and patient experience. Prescribers following recommendations to select needles on cost alone could overlook this. More generally, recommendations to select the lowest cost device creates a disincentive for manufacturers to continue to innovate products and services that can add significant value for patients and	inclusion criteria set for the relevant review. 3. The aim of NICE guidelines is indeed to take a holistic view, and in fact the GDG consider the evidence at *both* an interventional level as well as a specific product level, to evaluate where any potential benefits and harms are shown. If there are technology appraisals (TAs) in existence for any of the interventions that are looked at in the guideline, we cross-refer to the guidance given in the appraisals, and so the guideline and the TAs work hand-in-hand. 4. We have amended recommendation 1.8.4. It now reads:

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				clinicians. We request the recommendation should be removed or modified to endorse a greater balance between all the factors that contribute to the selection of a particular needle, which we interpret as being the intention of the guideline group.	After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]
Northumbria Healthcare NHS Trust	FULL	General	General	These comments from the UK DAFNE Collaborative include contributions from our user group as well as healthcare professionals who are members of our Executive Board. We believe this type 1 diabetes update is an excellent document and are particularly pleased to see even more emphasis placed on structured education and the quality assurance components required. With regard to the separation of structured education recommendations from insulin regimen guidance – we wonder whether the GDG have considered the possibility that the efficacy of certain (particularly basal) regimens might be dependent on the education provided on dose adjustment for users, and that much of the data considered both on education programmes and on comparison between insulin types	Thank you. We agree that regimens and how patients use them are at least as important, and probably more so, than the insulins used; and that MDI is likely to be effective only in the context of education and skills transfer – as we recommend everyone should have education (see recommendation 1.3.1). Unfortunately most of the studies do not report whether the recruited patients had had previous education or not. Two of the studies in the education review do mention in their

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				and regimens may be seriously confounded by this issue, which could have implications for the conclusions drawn from the meta-analysis.	inclusion criteria that they had not previously received any education. However, the nature of the randomisation process would mean that confounders, such as the amount of education given, should be equally balanced in all arms of the trial. This is one of the main reasons that we consider RCT evidence first for NICE guidelines when assessing interventions. We also used a random effects model in the NMA to account for any residual heterogeneity between the trials. Additionally, the GDG consider all these aspects (such as insulin doses, levels of education, and other confounders) in their critical analysis of the studies / evidence, and take this into consideration when weighing up the evidence in order to make a recommendation.

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Royal National Institute of Blind People	FULL	General	General	**Equalities Act 2010:** We believe that all NICE work should reflect the duties of public bodies under the Equalities Act 2010, not just in relation to communication and accessible information, but in relation to non-discriminatory treatment. We would expect NICE to take steps to meet their legal obligations. This not only requires public bodies to have due regard for the need to promote disability equality in everything they do - including the provision of information to the public - but also requires such bodies to make reasonable adjustments for individual disabled people where existing arrangements place them at a substantial disadvantage.	Thank you for your comment. The NICE publication 'developing NICE guidelines: the manual' https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf sets out how NICE meets its due regard duties under the 2010 Equality Act. We have added the following recommendation to support equality; Take account of any disabilities, including visual impairment, when planning and delivering care for people with type 1 diabetes
Royal National Institute of Blind People	FULL	General	General	**Accessible information:** We believe this guideline should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read	The NICE website has been built and tested to make sure it can be accessed and used by most people. NICE aims to comply with Web Content Accessibility Guidelines 1.0, Level Double-A. This means that

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				English." The Equality Act expressly includes a duty to provide accessible information as part of the reasonable adjustment duty. Online information on websites should conform to the W3C's Web Accessibility Initiative Web Content Accessibility Guidelines (WCAG) 1.0, level AA, as required by the NHS Brand Guidelines and the Central Office of Information. With regard to the accessibility of print materials, including downloadable content such as PDF files, we would request that wherever possible they comply with our "See it Right" guidelines: http://www.rnib.org.uk/professionals/accessibleinformation/Pages/see_it_right.aspx	most content, including NICE guidance products, is accessible to people with a visual impairment, through browser tools. These tools include converting written words to spoken words and being able to view text at larger sizes. Requests for information in alternatives formats such as audio or braille are considered on an individual basis and will be provided wherever possible.
Royal National Institute of Blind	FULL	General	General	We welcome the guidelines on Diabetes diagnosis and management, particularly the section entitled 'Managing Complications, eye disease'. However, we would like this guideline to include or provide more information on	Thank you, we agree with your comments. We have added the following

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People				the following: 1. Diabetic Retinopathy Screening- It is recommended everyone with diabetes should have an annual retinal screening with digital photographs. 2. Visual impairment or sight loss through Diabetic Macular Oedema can hamper a person's ability to self manage their diabetes. Most diabetics undertake daily activities in order to manage their condition. If they have vision loss/impairment they may require specifically developed technologies, assistance, or may even need to learn new techniques to undertake these daily activities. Vision loss/impairment means it is harder for a diabetic patient to: • Self administer insulin or use an insulin pump (where required) • Take tablets to manage their blood glucose levels (where required) and monitor their glucose levels at home • Check their feet daily for discolouration, as this could be a warning sign of a foot ulcer. The more significant the vision	recommendation: 1.2.1 Take account of any disabilities, including visual impairment, when planning and delivering care for people with type 1 diabetes We have changed recommendation 1.15.7 to say annually. We have amended recommendation 1.15.4. it now reads: Offer digital retinopathy screening annually to all adults with type 1 diabetes We refer readers to the DVLA guidance in recommendation 1.6.11.

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				loss the more difficult this will be for the patient. • Stay active to maintain a healthy weight • Eat a healthy, balanced diet and read food labels to identify products that are high in fat, salt and sugar. Patients may find it hard to read 'use by dates' on products or read cooking instructions. • diabetic patients often have to attend multiple medical appointments each year, which can have a huge impact on their life. For those with diabetes and visual impairment/sight loss appointment information should be delivered in a preferred format. • RNIB and RCO have produced an understanding series for Diabetes DVLA requirements for driving with Diabetes. Please refer individuals to GOV.UK document entitled 'At a glance guide to the current medical standards of fitness to drive'.	
Coeliac UK	FULL	General	General	• NICE guidelines for the treatment and	The GDG do not feel that these recommendations are contradictory.

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				management of coeliac disease are currently under consultation with publication anticipated in September 2015. The Type 1 diabetes update and coeliac disease update should be harmonised to ensure consistency within guidelines.	The new recommendation in the coeliac guideline says *'offer serological testing (for coeliac disease) to – adults and children with type 1 diabetes, at diagnosis.'* A person could have the test once (in keeping with coeliac guideline) and then again a few years later if they develop unexplained weight loss (i.e. our Rec 1.12.1 *'In adults with type 1 diabetes who have a low BMI or unexplained weight loss, assess markers of coeliac disease. [2004]'* Coeliac disease is not in our scope. We have referred this matter to the NICE guideline surveillance team.
Abertawe Bro Morgannwg University	FULL	General	General	We welcome the review of the NICE Clinical Guideline (CG) 15 for type 1 diabetes (T2DM) and support most of the recommendations that are made.	Thank you for your comments.

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Health Board				This response highlights some of the areas where clinical opinion within Swansea NHS Trust (as represented by the consultant body in diabetes & endocrinology) is at odds with the draft recommendations.	
Abertawe Bro Morgannwg University Health Board	FULL	General	General	The draft CG is at times utopian, in that its glycaemic targets are probably unachievable, it recommends a frequency of review that, in the current financial climate, is unrealistic and recommendations such as structured education is delivered by 'trained educators who have an understanding of educational theory' are risable in the context of some Health Boards in Wales providing no structured education whatsoever. Whilst one can argue it is appropriate to be aiming for the best care possible, the danger is that already over-worked, under-resourced staff are chastised for not achieving impossible goals.	Thank you for your response. Recommendations are designed to be in the best interest of patients. It is the responsibility of the health board to provide services to deliver them. People with type 1 diabetes should be supported by professionals who are suitably qualified. NICE is developing tools to support implementation and costing.
Royal	FULL	Genera	Gener	The draft guidelines are welcome but are sizeable and	NICE does not produce user-specific

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College of General Practitioners		l	al	are unlikely to be widely read in primary care. It may be useful to have a summary of significant changes and changes that are specific for primary care. Primary care health care professionals need immediate access to finger prick blood testing for accessing ill patients in the GP surgery or in the community. In primary care there are issues of calibration of handheld meters which can reduce the availability of machines.	versions (except for patients & carers). The short version of the guideline is a concise version of the guideline.
MedTech Europe	FULL	General	General	We have been asked by our members to provide a comment on the draft guideline for Type 1 Diabetes in adults and would like to thank NICE for the opportunity to do so. For the most part, the recommendations included in the draft guideline are fairly balanced and the Guideline Development Group should be recognised for their efforts in undertaking the enormous task of bringing together a very large amount of information on a wide range of topics associated with the management of diabetes. However, there are some areas we would like comment on that are relevant to the way in which NICE performs its role generally, and has some broader implications for the medical technology* industry.	Thank you for your comments..

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				** Medical technology is defined in this MedTech Europe response to include medical devices and in vitro diagnostics.*	
Glasgow Victoria Infirmary Diabetes Department	FULL	general	general	We feel there is a problem created by the separation of guidance on structured education from the guidance on basal insulin choice. This leads to apparent inconsistencies in approach and perhaps to an over-reliance on the basal insulin metanalysis. We have given more detail of our concerns in the comments below.	Thank you for your comment. We have responded to the issues raised in comment 297
Newcastle Upon Tyne Hospitals NHS Foundation Trust	FULL	General	General	In general we feel the guidelines are well put together and evidenced where appropriate but with a few specific inclusions which we feel lack unbiased evidence .In particular the promotion of twice dailt detemir as the initial basal insulin over other long acting "basal insulins in particular glargine , the suggestion that insulin pumps have a particular benefit in those with HbA1c >70 mmol/l and a lack of consideration of particular glycaemia targets of people with long duration type 1 diabetes particularly those with high risk of severe hypoglycaemia .	Thank you. The recommendation in favour of detemir is explained at length in the full guideline (see section 9.2.1). The recommended HbA1c target will need adjustment in individual circumstances, and this is covered in recommendations 1.6.7 & 1.6.8. The recommendations on Insulin pumps are taken from the NICE TA151 and were not updated as part of the production of this guideline.
Newcastle	FULL	Genera	54	In the recommendation to use rennin-angiotensin	Thank you for your comment.

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Upon Tyne Hospitals NHS Foundation Trust		I		blockade as first line in those with high blood pressure or nephropathy it should be stated that this may not be the first line drug of choice in those of black ethnicity and in the elderly .	This is an old recommendation and the question was not prioritised for review. The GDG discussed the recommendation in the absence of a detailed evidence update, and although they acknowledged that ACE-inhibitors may be less effective in controlling blood pressure than other agents when used in some ethnic groups or in the elderly, they were less sure about differences in relation to their value in renal protection. Without being sure how to amend the recommendation, it was judged safer to leave it unchanged but clearly marked as from the original CG15. This matter has been flagged to the NICE guideline surveillance team.
MedTech Europe	FULL	1 2.5	17 21	In general, we believe the guideline could be strengthened through clarification of the specific issues and challenges to be addressed. Recognition of and	Thank you for your comment. Specific issues to be addressed are included in the scope. We do not

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				reference to current levels of adoption of existing guidelines and technology appraisals and clarification of the gap that the guideline will address would be highly welcomed.	have data to assess the current level of adoption of existing guidance.
National Diabetes Nurse Consultant Group	FULL	1.14.1	38	Target range 5-8 mmol/s – too many variables in hospital setting to sometimes safety achieve this.	Thank you for your comment. This is a target and it is recognised that targets may not always be achieved. Nevertheless, the recommendation is based on evidence that setting these as targets has benefit.
National Diabetes Nurse Consultant Group	FULL	1.14.3	39	Suitability of IV insulin which could be used for longer periods in e.g. sepsis, high dose steroids	Thank you for your comment. The comment does not seem to relate to section 1.14.3 in the full guideline. We believe you are referring to recommendation 1.14.3 in the NICE guideline and have responded accordingly. The period of use of IV infusion should always be minimised but as long as clinically indicated. We believe our text covers the question.
National Diabetes	FULL	1.14.4	39	Inclusion of Consider- national DKA guidance recommends continuation of Basal insulin- would be	Thank you for your comment. 'We use 'consider' when we are confident

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Nurse Consultant Group				clearer if consider not included Safety issues relating to patient potentially being able to use CSII post surgery?	that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient. The use of 'consider' in this instance reflects (a) the paucity of firm evidence of benefit for continuing basal insulins during acute illness but the principle that with today's longer acting and less peaked basal insulins, continuing them during short periods of illness may help accelerate a stable conversion to

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					pre-morbid insulin regimens after the acute event; and (b) in the case of CSII, the recognition that the basal rate is equivalent to the basal injected insulin, and that, where appropriate expertise is available, this can be continued during acute illness, especially in centres where the DKA regimen expects basal insulin continuation. The use of the word "consider" means that each unit can make a final decision on how to adopt this recommendation either generally or on a patient-by-patient basis. The same rationale applies to the suggestion that continuing basal insulin replacement in whatever form it is usually taken after during acute illness. Local protocols should take into account local expertise, and it is reasonable to use CSII as basal

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					replacement in situations where the patient is unable to self-administer if the health care team is experienced in such usage.
National Diabetes Nurse Consultant Group	FULL	1.4.2	20	Evidence to support need for course for CHO counting when patients are already awaiting another course?	Thank you for your comment. This is explained in the 'linking evidence to recommendations' section in the full guideline (please see section 7.3.6).
Welsh Endocrine and Diabetes Society	FULL	1.10.6	General	In section 1.10.6 "Avoid relaxing individualised blood glucose targets as a treatment for adults with type 1 diabetes with impaired awareness of hypoglycaemia. [new 2015] " This may need further qualification. Some patients will have elected to have blood glucose targets which are too low and are contributing to the hypoglycaemia and therefore need relaxing.	Thank you for your comment. We have added a recommendation: *Where patient preferred targets are lower than recommended, the NICE target should be reinforced*
National Diabetes Nurse Consultant Group	FULL	1.10.6	31	Could be misleading to none specialist health care professionals	Thank you for your comment. We have added a recommendation: *Where patient preferred targets are lower than recommended, the NICE*

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					target should be reinforced
National Diabetes Nurse Consultant Group	FULL	1.6.13	25	Should include insulin pump therapy	Thank you for your comment. The guideline development group reviewed the evidence for this and found no evidence to suggest that use of CSII mandates more frequent testing (unless other circumstances apply, as outlined in the recommendation).
Training, Education and Research for Nurses in Diabetes UK	FULL	1.7.12	29	No mention of education in injection technique including rotation of sites, needle length. Impact of poor injection technique on glycaemic control and safety is under-emphasised. Include a comprehensive assessment of injection technique and examination for lipohypertrophy. Include 'using correct procedure to examine for lipohypertrophy'. Lipohypertrophy is under-reported as many HCPs don't know what they are looking for. (Blanco et al Diet & Metabolism, 2013)	Thank you for your comment. Site rotation is covered in recommendation 1.8.5 in the short version of the guideline. Needle length is addressed by recommendation 1.8.3. Lipohypertrophy was not prioritised by stakeholders during the scoping phase and was not included in the scope. This matter has been referred to the NICE guideline surveillance team,

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					Further explanation is provided in the full version of the guideline (please section 9.3).
NHS England	FULL	1.7.3	General	Do not offer non-basal–bolus insulin regimens for treating adults newly diagnosed with type 1 diabetes. [new 2015]. This is quite a definitive recommendation in the NICE Guideline, despite the Full Guideline acknowledging lack of evidence one way or the other on which insulin regimen is best on initial presentation, as well as the acknowledgement that twice daily mixed insulin may be preferable for some individuals to get used to injecting insulin. Perhaps the option of twice daily mixed insulin should be permitted temporarily in selected individuals on first presentation with Type 1 diabetes.	Thank you for your comment. We agree the recommendations are definitive and this is as intended by the guideline development group. While individual items of evidence are not always of high quality, we based our recommendations on reviewing it as a whole. The guideline is designed to provide indications of best management. There will always be patients in whom alternative strategies are indicated. We allow for patient choice and healthcare professional judgement in recommendation 1.7.10.

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National Diabetes Nurse Consultant Group	FULL	1.7.3	27	Basal bolus may not be suitable in some cases, elderly patients, needle phobia etc.	Thank you for your comment. We agree the recommendations are definitive and this is as intended by the guideline development group. While individual items of evidence are not always of high quality, we based our recommendations on reviewing it as a whole. The guideline is designed to provide indications of best management. There will always be patients in whom alternative strategies are indicated. We allow for patient choice and healthcare professional judgement in recommendation 1.7.10.
Training, Education and Research for Nurses	FULL	1.7.3	27	What about patient choice – you cannot force a patient to have basal bolus regimen especially if elderly.	Thank you for your comment. We agree the recommendations are definitive and this is as intended by the guideline development group. While individual items of evidence

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in Diabetes UK					are not always of high quality, we based our recommendations on reviewing it as a whole. The guideline is designed to provide indications of best management. There will always be patients in whom alternative strategies are indicated. We allow for patient choice and healthcare professional judgement in recommendation 1.7.10.
NHS England	FULL	1.7.45	General	gives very clear preference to detemir over glargine. This however does not well reflect the experience of clinical practice. In order to achieve 4 injections a day rather than 5 with a basal bolus regimen, many clinicians perceive that glargine has advantage over detemir as a once daily basal insulin. If it becomes clinically apparent that the individual needs twice daily basal insulin, then the frequency of either can then be increased. However, the need to do this is perceived by many to be less with glargine, giving it a perceived	Thank you for your comment. We accept that there is a widely held perception that once daily basal insulin is preferable for patient convenience but there was no evidence in the literature to support this. In the absence of data on twice daily glargine, we are unable to recommend it, and we considered twice daily glargine not clinically

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				advantage. The recommendation that detemir is used in preference to glargine is based on trial data of twice daily detemir; twice daily detemir has been compared only with once daily glargine rather than twice daily glargine. Trials of twice daily glargine may be lacking because there is less need, if using it as the basal insulin, to give it twice daily. It would be preferable if the guideline recommended either.	relevant as it is not in common use. The guideline supports the use of once daily glargine if patients express the desire to avoid an extra injection in a MDI regimen.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.6.5	24	Fructosamine is not an easily available test - when iresult is obtained it is usually too late to be useful in many areas.	Thank you for your comment.. We accept your comment, however fructosamine testing still has a place as outlined in the recommendation.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.8.3	30	There is no clinical evidence to offer any greater than 6mm needle in adults (Schwartz S et al 2004)	Thank you for your comment. A single study is quoted, comparing 6mm with 12.7 mm needles only. Please see section 9.3 of the full guideline which covers several studies and a greater variety of needle sizes.

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National Diabetes Nurse Consultant Group	FULL	1.6.6 1.6.7	24	Statements could be confusing for non-specialist health care professionals. Concern regarding tightness of target	Thank you for your comment. This was not the intention. We accept the wording does not distinguish between a target and an achieved value. We have amended the recommendation
Training, Education and Research for Nurses in Diabetes UK	FULL	1.6.6	24	1.6.8 contradicts this statement. Statement is too broad – needs to state where safe.	Thank you for your comment.We disagree with this statement. In the full guideline we have referred to the evidence that shows that lower HbA1c can be achieved with lower hypoglycaemia risk through structured education in flexible insulin therapy.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.8.4	30	Lowest acquisition cost may be of poor quality – if needles are reused against HCP advice there may be a risk of breakage – very costly to NHS and patient	Thank you for your comment. We have amended recommendation 1.8.4. It now reads: After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and

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					reusable insulin pen injectors.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.8.4	30	What does "If possible" mean?	Thank you for your comments. 1. Issues to be addressed are set out in the guideline scope 2. Our methodology considered all these factors, by critical review of the data we analysed. The methodology used in the guideline is highly robust and reflects that of both Cochrane and GRADE methodology (including the issues of blinding). We conduct critical reviews of the evidence and consider all of the factors that you mention, and so we are glad that you agree with our methodology. With regards to blinding, even though it may not be possible for a study to be

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					blinded, the fact that there is lack of blinding can still lead to /introduce bias, and so the evidence has been appropriately downgraded for being at 'risk' of bias. In response to your comment about including the most recent evidence. Our literature searches are rerun 8 weeks before the guideline goes out for consultation, and so recently published study data is captured and 3. The aim of NICE guidelines is indeed to take a holistic view, and in fact the GDG consider the evidence at *both* an interventional level as well as a specific product level, to evaluate where any potential benefits and harms are

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					shown. If there are technology appraisals (TAs) in existence for any of the interventions that are looked at in the guideline, we cross-refer to the guidance given in the appraisals, and so the guideline and the TAs work hand-in-hand. 4. We have amended recommendation 1.8.4. It now reads: After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]
Training, Education and Research for Nurses	FULL	1.8.5	30	Poor knowledge among HCPs on correct rotation advice – see	Thank you for your comment. Poor knowledge among healthcare professionals on correct rotation advice is regrettable. However, this is an issue for implementation rather

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in Diabetes UK					than the guideline.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.8.6	30	Not every area in UK has suitable of safe disposal system as outlined in EU Directive 2010/32 transferred to UK Law in 2013.The First UK Injection Technique Recommendations 2011 currently being updated.	Thank you for your comment. Safe sharps disposal should be made available. This is an implementation issue that will be passed onto the implementation team.
Training, Education and Research for Nurses in Diabetes UK	FULL	1.8.7	30	More emphasis required on checking for lipohypertrophy – evidence of increased cost to NHS and patient if poor injection technique. Include a comprehensive assessment of injection technique and examination for lipohypertrophy.	Lipohypertrophy was not prioritised by stakeholders during the scoping phase and was not included in the scope.
MedTech Europe	FULL	3.2	31	With respect to the collection and interpretation of evidence we would like to highlight the following points: - (strength of) evidence related to medical technology needs to be assessed using an appropriate methodology, taking into account specifics related to medical technology. Using a methodology designed for pharmaceuticals may lead to misleading or	Thank you for your comment. The methodology used in the guideline is highly robust and reflects that of both Cochrane and GRADE methodology (including the issues of blinding). We conduct critical reviews of the evidence and consider all of the

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				inaccurate conclusions/results. For example, studies appear to have been graded as low quality partially because they were not blinded. This is not practical for many medical technologies. As literature searches are time defined, ways need to be developed to include the most recent evidence in NICE guidelines – this would ensure published guidance being in line with the most recent clinical evidence.	factors that you mention, and so we are glad that you agree with our methodology. With regards to blinding, even though it may not be possible for a study to be blinded, the fact that there is lack of blinding can still lead to /introduce bias, and so the evidence has been appropriately downgraded for being at 'risk' of bias. In response to your comment about including the most recent evidence. Our literature searches are rerun 8 weeks before the guideline goes out for consultation, and so recently published study data is captured and incorporated where appropriate.
Roche Diagnostics	Full	4.2	61-62	The recommendations 51 and 53 are redunant.	**Thank you for your comment. We have deleted the duplicated recommendations.**
Royal	FULL	4.1.1	52	Suggest adding 'if appropriate' to top right hand box.	Thank you for your comment.

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College of Physicians of Edinburgh				The importance of recognising the special needs of people who have had longstanding T1DM (e.g. for over 40 years) is being increasingly recognised. In this group, the risk of harm from serious hypoglycaemia far outweighs the benefits of lowering average blood glucose. This group of individuals is growing rapidly in number and, in order to avoid the harm that the standard guideline approach can bring about, it is absolutely vital to flag up the existence and special requirements of this group. The upper and lower boxes which terminate at the lower line should be amended so that the target becomes 'should usually be'.	We accept the statement about needs. We have allowed for this in the recommendation about individualised targets (1.6.7 in the short version). This is a matter of clinical judgement and patient choice.
	Full	4.2	55	"Enable adults with type 1 diabetes who are hospital inpatients to self-administer subcutaneous insulin if they are willing and able and it is safe to do so." If not, please consider CSII as an option.	Thank you for your comment. This recommendation does not preclude the use of CSII, which is a subcutaneous route of administration, and therefore encompassed by the recommendation.
NHS South Sefton	FULL	4.1.2	53	The use of twice daily Detemir insulin as the preferred long acting insulin is unlikely to be tolerated by patients	Thank you for your comment. In the context of structured education,

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CCG				as this will mean at least five injections a day. This is unlikely to improve concordance and result in an increased number of complications associated with poor glycaemic control.	adults with type 1 diabetes are usually able to understand the benefits and disbenefits of a twice daily basal insulin regimen. NICE has produced separate guidance on medicines adherence https://www.nice.org.uk/guidance/cg76
Novo Nordisk Ltd	FULL	4.1.2	53	**Algorithm, Long-acting insulins:** Novo Nordisk supports the committee's decision to place twice daily insulin detemir (Levemir®) as first line for basal insulin replacement. • The guideline suggests insulin glargine as an option if patients do not want twice daily injections. However the insulin detemir license states 'The duration of action is up to 24 hours depending on dose providing an opportunity for once or twice daily administration.' Therefore we would suggest that the wording allows for consideration of once daily insulin detemir before changing the patient to	Thank you for your comment. We have revised the recommendation which now gives the option of once daily detemir or glargine if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. This was based on the revised economic analysis.

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				another insulin	
Novo Nordisk Ltd	FULL	4.1.2	53	**Algorithm, Long-acting insulins:** Novo Nordisk notes the omission of insulin degludec (Tresiba®) from the treatment algorithm and request that it is included as an option for certain patient populations that would benefit from this insulin. • Insulin degludec is a basal insulin with a long duration of action and stable action profile that results in a glucose lowering effect beyond 42 hours and a lower day-to-day variability in glucose-lowering effect compared with insulin glargine (Tresiba® SPC) • This pharmacodynamic profile is associated with important clinical benefits compared to currently marketed basal insulin analogues. Insulin degludec has a half-life of more than 25 hours in type 1 and type 2 diabetes patients. This is twice as long as insulin glargine, which has a half-life of 12.5 hours (Heise T, et al, Diabetes 2011; 60 (Suppl. 1A): LB11.). More importantly, it may allow patients to	Thank you for your comment. The Heller study was included in our review, while the Vora systematic review was not included as it was a systematic review which we use only as sources of references. Our network meta analysis (NMA) did not show any beneficial effect for degludec in terms of major/severe hypoglycaemia compared to other strategies. We have now included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus

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				improve glycaemic control with less risk of hypoglycaemia, particularly nocturnal confirmed hypoglycaemia when compared with insulin glargine. The lower rate of nocturnal confirmed hypoglycaemia was shown compared with insulin glargine in basal–bolus therapy in Type 1 diabetes. This is in addition of a significantly lower dose of both basal and bolus insulin. (Heller S, Lancet 2012;379:1489-1497) • Insulin degludec enables patients who miss a scheduled dose to administer it when it is discovered (ensuring a minimum of 8 hours between injections of insulin degludec) without increasing the risk of hypoglycaemia (Tresiba® SPC) • In a meta-analysis in type 1 diabetes, the overall basal-bolus insulin dose for insulin degludec versus insulin glargine was 12% lower (13% lower for basal insulin daily dose and 12% lower for bolus insulin dose). Ref: Vora et al. Insulin Degludec Versus Insulin Glargine in Type 1 and Type 2 Diabetes	detemir for the same outcome measure. However this was from a single very small study and the evidence was graded as low quality. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. This was the case also in a sensitivity analysis where the average insulin doses from the RCTs included in the network meta-analysis were used. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: **"Use other basal insulin regimens for adults with type 1 diabetes only if the regimens in**

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				Mellitus: A Meta-Analysis of Endpoints in Phase 3a Trials. Diabetes Ther, 2014. DOI 10.1007/s13300-014-0076-9 • The delivery device for insulin degludec (FlexTouch®), has shown consistency and accuracy of dose delivery with significantly lower injection force than comparator pens (Hemmingsen H, Diabetes Technol Ther 2011; 13:1207–1211) Choice of all available insulin options is important for both clinicians and patients. Novo Nordisk requests that insulin degludec is presented as a clear treatment option in Type 1 diabetes and incorporated into the algorithm to reflect this as per its acknowledgement in the full guideline section 9.2.1 (p257). Type 1 diabetes patient populations who may benefit from insulin degludec include those who: ➢ are experiencing recurrent hypoglycaemia, particularly nocturnal, including those potentially considering continuous subcutaneous insulin infusion (CSII) therapy	**recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost".**

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				➢ are experiencing persistent hyperglycaemia requiring acute treatment where other treatment options are not providing adequate control ➢ would medically benefit from the flexibility in dose timing on occasion, such as those with irregular lifestyles or those requiring third-party assistance to administer their insulin ➢ currently administer two doses of a long-acting basal insulin analogue each day	
Novo Nordisk Ltd	FULL	4.3	53	Algorithm, Rapid-acting insulins: Novo Nordisk supports the committee's decision to place insulin aspart (NovoRapid®) as first line for bolus insulin replacement.	Thank you for your comment.
Medtronic	FULL	4.3	62	The clinical and cost-effectiveness of continuous glucose monitoring (CGM) as a stand-alone technology was assessed within the guideline, however the use of CGM integrated with a sensor-augmented insulin pump system was not considered. Some current sensor-augmented pump systems incorporate a predictive low glucose suspend feature; these systems are currently under assessment within the NICE Diagnostic	Thank you for your comment. We looked at CGM vs. SMBG as outlined in the scope and included all studies that addressed this (whether CGM alone or integrated systems). We believe our recommendations allow for the use of CGM in the

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				Assessment Programme (DAP). The combination of CGM and insulin pump therapy, particularly those pumps equipped with an automated low glucose insulin suspension system, has been shown to improve glycaemic control relative to insulin pumps alone (Battelino et al., 2012), and reduce the rate of nocturnal hypoglycaemic events, the fear of which can cause significant distress for some patients (Choudhary et al., 2011; Bergenstal et al., 2013). The sensor augmented pump system is also clinically effective in patients with impaired awareness of hypoglycaemia, with authors reporting a reduced incidence of severe hypoglycaemic events with this system versus insulin pumps alone (Ly et al., 2013). Further, there is emerging evidence to suggest that across various geographies the sensor augmented pump system is cost-effective compared with insulin pump therapy alone, including in Sweden (Roze et al., 2014), Australia (Ly et al., 2014), and the UK (Roze et al., 2015; manuscript in submission). As the current draft guideline has only assessed CGM as a stand-alone device, and the clinical or economic	circumstances in which you are suggesting the sensor augmented pump will be beneficial and therefore allow for this. The forthcoming NICE diagnostic assessment will give further on the more specific risk:benefit issues. All of the references you have provided were considered as part of our review and those meeting the inclusion criteria were included.

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				benefits of this therapy when used within the sensor augmented pump system with low glucose suspend were not considered, we feel it would be pertinent to remove recommendation #56 in order to avoid any undue confusion when the DAP recommendations are published. This would avoid any future contradictory statements with the DAP recommendations, should the outcomes for the sensor augmented pump system differ to stand-alone CGM. The subsequent statements outlining the criteria for which subgroups of patients should be considered for CGM sufficiently ensures that CGM would not be offered routinely in any case, therefore we propose that recommendation #56 could be removed altogether without significantly altering the key advice from NICE. If it is not possible to remove this recommendation, we politely request that, at the minimum, this statement is re-worded to more precisely reflect what was assessed within the guideline, and ensure clear alignment with the DAP appraisal. A specification suggestion is as follows:	

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				• *'Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes as a stand-alone therapy. Please refer to the NICE Diagnostic Assessment Programme report for specific recommendations on continuous glucose monitoring when used in conjunction with a sensor augmented insulin pump.*' References Battelino T, Conget I, Olsen B, et al. (2012). The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia. 55:3155-62 Choudhary P, Shin J, Wang Y, et al. (2011) Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. Diabetes Care. 34:2023-5 Bergenstal RM, Klonoff DC, Garg SK, et al. (2013)	

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				Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 369:224-32 Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. (2013) Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. JAMA. 310:1240-7 Ly TT, et al. (2014). A cost-effectiveness analysis of sensor-augmented insulin pump therapy and automated insulin suspension versus standard pump therapy for hypoglycemic unaware patients with type 1 diabetes. Value Health. 2014 Jul;17(5):561-9. Roze S, Saunders R, Brandt A, de Portu S, Papo NL, Jendle J. (2014). Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. Diabet Med. doi: 10.1111/dme.12661. [Epub ahead of print] Roze S, et al.(2015). Long-term health economic	

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				benefits of sensor augmented pump versus continuous subcutaneous insulin infusion alone in type 1 diabetes: a UK perspective. In submission to Diabetologia (data on file).	
Medtronic	FULL	4.3	62	We welcome this recommendation as it is clear that a cohort of patients can benefit from real-time CGM, however, we feel that the statement regarding '*adults…who are willing to commit to using it at least 70% of the time'* sets an uncompromising target that may restrict patients that could otherwise benefit. We agree that >70% usage of CGM should be recommended, yet in order to recognise that some patients may not be able to always achieve >70% usage owing to various circumstances we respectfully suggest that this statement is re-worded to: • '*Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are aiming to use it at least 70% of the time and to calibrate it as needed, and who have any of the following that persist despite optimised use of insulin therapy and conventional blood*	Thank you for your comment. After careful consideration, we do not agree the wording should be changed as the GDG believes the technology is relatively expensive and it would not be a good use of resources to provide it to an individual who is not committed to engaging fully in its use. The evidence supports that benefit is seen only in those using it 70% of the time.

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				glucose monitoring:' As per the previous comment, we believe that clarity around stand-alone CGM versus integrated CGM with a sensor augmented insulin pump should be provided in this recommendation statement i.e. should both options be considered?	
Medtronic	FULL	4.3	62	Regarding the specific patient groups mentioned in this statement, the previous Clinical Guideline (CG15, 2004) included recommendations on CGM for episodes of hyperglycaemia, yet this has now been removed and hyperglycaemia is no longer a criterion for CGM consideration. We propose that hyperglycaemic events should be re-instated within the criteria for CGM consideration, as there are clinical data to demonstrate the effectiveness of CGM for hyperglycaemia. Further, patients with poor control of HbA1c should also be included as a subgroup for consideration of CGM, particularly when used in conjunction with the sensor augmented pump system. Indeed, NICE	Thank you for your comment. We have appropriately incorporated the Pickup 2011 data into our meta-analysis and it does not change the results of the meta-analysis or those of the economic analysis. For this reason the GDG decided not to change the recommendation. We did look at data for CGM for hyperglycaemia and that given the recommendation of supporting increased frequency of SMBG, the evidence does not suggest CGM is a

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				recommendation 1.6.23 states that CGM should be used a part of strategies to optimise HbA1c, therefore the addition we suggest would serve to make the recommendations consistent throughout. Several authors have reported significant reductions in HbA1c with no increased risk of hypoglycaemia when CGM is used in addition to insulin pump therapy with the low glucose suspend feature, compared with a standard insulin pump (Ly et al., 2013; Battelino et al., 2012; Pickup 2011, JDRF 2008). In a recent meta-analysis, Pickup (2011) demonstrated the efficacy of CGM in reducing HbA1c compared to Self-Monitoring of Blood Glucose (SMBG) levels in 449 patients from six randomised trials. CGM was associated with a significant reduction in HbA1c, with the greatest reductions observed in patients with the highest HbA1c at baseline, and in patients who used the sensors most frequently (Pickup, 2011). Further, in the meta-analysis regression, Pickup (2011) illustrated that for a patient with a baseline HbA1c of 10.0% can expect about a 0.9% HbA1c improvement with CGM therapy when sensors are used daily, while reducing	cost effective alternative to SMBG up to ten tests per day. We conducted a sensitivity analysis where we assumed CGM was able to reduce HbA1c to 6%. This did not change the results.

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				exposure to hypoglycaemia at the same time. References Battelino, T. et al., 2012. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia, 55(12), pp.3155–62. JDRF, 2008. Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes. N Engl J Med, 394(14). Ly, T.T. et al., 2013. Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump Therapy on Hypoglycemia in Patients With Type 1 Diabetes A Randomized Clinical Trial. , 310(12), pp.1240–1247. Pickup, J.C. & Freeman, S.C., 2011. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose : meta-analysis of randomised controlled trials	

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				using individual patient data. BMJ, pp.1–14.	
Medtronic	FULL	4.3	62	We fully agree with this recommendation, and feel that this reinforces the need to include 'poor control of HbA1c' as a criterion within recommendation #57 (please see previous comment).	Thank you for your comment. We have appropriately incorporated the Pickup 2011 data into our meta-analysis and it does not change the results of the meta-analysis or those of the economic analysis. For this reason the GDG decided not to change the recommendation. We did look at data for CGM for hyperglycaemia and that given the recommendation of supporting increased frequency of SMBG, the evidence does not suggest CGM is a cost effective alternative to SMBG up to ten tests per day. **We conducted a sensitivity analysis where we assumed CGM was able to reduce HbA1c to 6%. This did not change the results.**
Medtronic	FULL	4.3	62	We urge that recommendation #64 regarding the use of	Thank you for your comments. This

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				CSII/insulin pumps is included in the 'Key Priorities for Implementation' section. This technology has a positive NICE Technology Appraisal (TA151) and as such, represents a cost-effective use of resources in the NHS. The projected uptake of CSII from NICE TA 151 published in 2008 have yet to be attained, and these projections were based on the prevalent patient pool only. NICE projected that an additional 13,761 patients in NHS England should receive a pump over a 4 year projection period (by 2012), which together with the existing insulin pump patient population would equate to treating 10% of adults and 25% of children with type 1 diabetes. A UK service level audit on insulin pump uptake published in 2013 (White et al., 2014) showed that: • Across the UK only 6% of adults with type 1 diabetes have received an insulin pump (13 428 adults), • The uptake of insulin pump therapy in the UK falls well below the projected levels set out in	is a Technology Appraisal, and as such it already carries mandatory implementation status. Therefore it is not appropriate to include it in the Key Priorities for Implementation.

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				the NICE TA 151, and that of other European countries (> 15%) and the USA (40%). By highlighting insulin pumps as a key priority for appropriate patients in the guideline, this will help to ensure that the TA151 is implemented and healthcare resources are used effectively. White et al., 2014. The UK service level audit of insulin pump therapy in adults. *Diabet. Med.* 31, 412–418.	
Novo Nordisk Ltd	FULL	4.3	62	Bullet no. 62, We would request that insulin detemir may be considered for once daily dosing before changing the patient's insulin if twice daily injections are not suitable. Evidence supporting this includes: Heller S et al, 2009. 31(10):2086-2097. Bartley P et al, Diabetic Medicine, 2008. 25:442-449. Vague P et al, Diabetes Care, 2003. 26(3):590-596. Zachariah et al, Diabetes Care, 2011. 34:1487-1491.	Thank you for your comment. All three studies mentioned in your comment have been included in our network meta-analysis. **We have revised the recommendation which now gives the option of once daily detemir or glargine if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. This was based**

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					on the updated economic analysis that was revised following consultation
Novo Nordisk Ltd	FULL	4.3	63	Bullet 71 – Novo Nordisk requests that insulin degludec be considered as an option for patients struggling with hypoglycaemia due to the randomised controlled trial evidence for reduction in hypoglycaemia, particularly nocturnal compared to insulin glargine as stated in the insulin degludec license.	Thank you for your comment. Our network meta analysis (NMA) did not show any beneficial effect for degludec in terms of major/severe hypoglycaemia compared to other strategies. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality.

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					Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: "Use other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost".
Medtronic	FULL	4.3	64	We welcome this recommendation as it is evident that fear of injections and the associated pain can have a detrimental impact upon insulin therapy adherence. The	Thank you. We are unable to include advice about ports, as these were not prioritised for review during

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				use of subcutaneous injection ports, which can accommodate multiple drug injections without the discomfort of additional needle sticks, can minimise the burden of daily injections thereby promoting treatment adherence. We propose that this recommendation makes specific reference to injection ports and their use in these patient groups i.e: • *'Provide adults with type 1 diabetes who have special visual and psychological needs, or who are experiencing fear and/or pain with multiple daily injections, with injection devices such as injection ports, or needle-free systems that they can use independently for accurate dosing.'* Authors of five randomised controlled trials (listed below) have demonstrated the clinical value of injection ports in the management of diabetes for patients who were prescribed multiple daily injections of insulin. Patient cohorts across these studies include children, adolescents and adults with either type 1 or type 2 diabetes.	scoping; however, this has been flagged to NICE's surveillance team.

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				Blevins et al. 2008. A Study Assessing an Injection Port for Administration of Insulin. Diabetes Spectrum Volume 21, Number 3, p. 127. Burdick et al. 2009. Use of a subcutaneous injection port to improve glycemic control in children with type 1 diabetes. Pediatric Diabetes; 10: 116–119 doi: 10.1111/j.1399-5448.2008.00449.x Rabbone et al. 2008. Intensive insulin therapy in preschool-aged diabetic children: From multiple daily injections to continuous subcutaneous insulin infusion through indwelling catheters. J. Endocrinol. Invest. 31: 193-195. Hanas et al. 2002. Indwelling catheters used from the onset of diabetes decrease injection pain and pre-injection anxiety. J Pediatr; 140:315-20 Hanas et al. 1994. Metabolic control is not altered when using indwelling catheters for insulin injections. Diabetes Care. 117(7):716-8.	

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Medtronic	FULL	4.3	65	We believe that a statement such as 'offering real-time glucose monitoring when used in conjunction with a sensor augmented insulin pump with low glucose suspend feature' should be included as a management strategy within this recommendation. In the ASPIRE study it was shown that the sensor augmented pump with low glucose suspend significantly reduced nocturnal hypoglycaemia, compared with insulin pump alone, without increasing HbA1c, in all patients wearing the sensor at least 70% of the time (1.5±1.0 vs 2.2±1.3 events per patient/week, p<0.05). Bergenstal RM, Klonoff DC, Garg SK, et al. (2013) Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 369:224-32	Thank you for your comments. We have reviewed the evidence for CGM. The forthcoming NICE Diagnostic Assessment will provide further guidance. By allowing CGM, we implicitly allow the use of any type of CGM system.
Novo Nordisk Ltd	FULL	4.3	65	Bullet 96 – Novo Nordisk requests that insulin degludec be stated as a treatment option here for nocturnal hypoglycaemia based on the randomised controlled trial evidence for reduction in nocturnal hypoglycaemia compared to insulin glargine (as stated above).	Thank you for your comment. Our network meta analysis (NMA) did not show any beneficial effect for degludec in terms of major/severe hypoglycaemia compared to other strategies. We have included

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					nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. We do acknowledge the variation in

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					individual response in real practice and therefore we have added a further recommendation: "Use other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost".
Roche Diagnostics	Full	4.4 8.3.2	75 234	When asking for evidence in adults with type 1 diabetes on clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters, we kindly ask the GDG to consider • multiple studies that have demonstrated the value of bolus advisors in insulin pump therapy (Bode, Sabbah et al. 2002, Klupa, Benbenek-Klupa et al. 2008, Zisser, Wagner et al. 2010, Enander, Gundevall et al. 2012) and • the benefits of bolus advisor use in MDI therapy: - Investigating the effect of flexible intensive	In relation to the studies you quote: • insulin pump studies were excluded from our scope (pumps covered by TA151) • Thank you for the Schmidt, Meldgaard reference. We note that use of a bolus calculator did not improve HbA1c any more than FIIT and CHO-counting without use of a bolus calculator.

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				insulin therapy (FIIT) and an automated bolus calculator (ABC) in a Danish type 1 diabetes population treated with MDI therapy, FIIT and carbohydrate counting were successfully taught in 3 hours and improved metabolic control and treatment satisfaction; concurrent use of an ABC improved treatment satisfaction further (Schmidt, Meldgaard et al. 2012). - Investigating whether use of an automated advisor (BA) might reduce fear of hypoglycemia and encourage patients to achieve improved glycemic control, most patients felt that using the BA was easier than manual bolus calculation, improved their confidence in the accuracy of their bolus dosage, and reduced their fear of hypoglycemia. (Barnard K 2011) - Determining if the use of an automated BA improves glycemic control in sub-optimally controlled, MDI-treated patients with type 1 and type 2 diabetes, more patients using automated bolus advice achieved >0.5% HbA1c reduction than the control (non-automated bolus advice-using) patients. Use of the BA was	**Regarding the other studies, treatment satisfaction alone was not one of our pre-determined primary outcome measures.**

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				associated with reduced glycemic variability but not with higher frequency of severe hypoglycemia. Overall, patients sought and accepted bolus advice frequently. In addition, use of a BA is associated with improved competency in carbohydrate counting, and test subjects using automated bolus advice showed significantly greater improvement in treatment satisfaction compared with control patients (Cavan, Ziegler et al. 2014); (Ziegler, Cavan et al. 2013); (Cavan, Ziegler et al. 2013); (Cavan, Ziegler et al. 2013); (Ryder, Cavan et al. 2013); (Ziegler, Rees et al. 2014)	
Roche Diagnostics	FULL	4.4 4.5	75 77	"What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?": The implementation of intensive insulin therapy accompanied by appropriate training implemented as part of a continuous quality-assurance programme is effective and safe in routine care. Improvement of glycaemic control can be achieved without increasing the risk of severe hypoglycaemia.(Samann, Muhlhauser et al. 2005)	Thank you for your comments. We agree.

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Roche Diagnostics	FULL	4.4 8.2.8	75 233	"Which therapies are effective in controlling postmeal plasma glucose? EVIDENCE STATEMENTS • Diets with a low glycaemic load are beneficial in improving glycaemic control [Level 1+] • Several classes of pharmacologic agents preferentially lower postmeal plasma glucose [Level 1+] RECOMMENDATION A variety of both non-pharmacologic and pharmacologic therapies should be considered to target postmeal plasma glucose. Question 4 What are the targets for postmeal glycaemic control and how should they be assessed? EVIDENCE STATEMENTS • Postmeal plasma glucose levels seldom rise above 7.8 mmol/l (140 mg/dl) after food ingestion in healthy non-pregnant people [Level 2++] • Self-monitoring of blood glucose (SMBG) is currently	Thank you for your comments. 'Which therapies are effective in controlling postmeal plasma glucose' is a research recommendation. The Guideline Development Group are proposing that more research is undertaken in this area.

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				the optimal method for assessing plasma glucose levels [Level 2++] RECOMMENDATIONS • Postmeal plasma glucose should be measured 1-2 hours after a meal • The target for postmeal glucose is 9.0 mmol/l (160 mg/dl) as long as hypoglycaemia is avoided. • Self-monitoring of blood glucose (SMBG) should be considered because it is currently the most practical method for monitoring postmeal glycaemia. Self-monitoring of blood glucose (SMBG) is currently the optimal method for assessing plasma glucose levels [Level 1++] SMBG allows people with diabetes to obtain and use information about "realtime" plasma glucose levels and facilitates timely intervention to achieve and maintain glycaemic control. SMBG in accepted as an integral part of diabetes management in people with diabetes requiring insulin therapy. Recently the IDF has published guidance on the use of SMBG in people with	

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				non-insulin treated diabetes and emphasized the need to ensure that there is an agreed purpose for using SMBG and that specific action should be linked to SMBG. (120) Recent studies have confirmed that structured SMBG followed by therapeutic interventions result in greater HbA1c reduction in people with non-insulin-requiring type 2 diabetes compared with programmes without structured SMBG. (121-123) SMBG is only one component of diabetes management. Its potential benefits require training of people to perform SMBG, interpret their test results and appropriately adjust their treatment regimens to achieve glycaemic control. Moreover, clinicians must be versed in interpreting SMBG data, prescribing appropriate medications and closely monitoring people in order to make timely adjustments to their regimens as needed. The timing and frequency of SMBG must be individualized to each person's treatment regimen and level of glycaemic control. (120)"(International Diabetes Federation 2011)	

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Roche Diagnostics	FULL	4.4	75	Langendam et al. have shown significant decreases of HbA1c in adults based on CGM in combination with MDI in combination of slight non-significant increase of severe hypoglycemia. (Langendam, Luijf et al. 2012). "Continuous glucose monitoring was associated with a significant reduction in HbA1c percentage, which was greatest in those with the highest HbA1c at baseline and who most frequently used the sensors. Exposure to hypoglycaemia was also reduced during continuous glucose monitoring. The most cost effective or appropriate use of continuous glucose monitoring is likely to be when targeted at people with type 1 diabetes who have continued poor control during intensified insulin therapy and who frequently use continuous glucose monitoring." (Pickup, Freeman et al. 2011)	Thank you for your comment. The GDG do not think that the current recommendations on CGM should change. The Langendham study is a Cochrane review. Our review is more up-to-date (the cut-off date for the Langendam review was 2011). In the economic analysis we also performed some sensitivity analyses whereby CGM was assumed to be more effective than SMBG at reducing hypo events and HbA1c. In these analyses CMG was still not cost effective.
Newcastle Upon Tyne Hospitals NHS Foundation Trust	FULL	7	56	The recommendation is not to measure pancreatic auto- antibodies and c-peptide routinely at diagnosis in people diagnosed with type 1 diabetes . The supporting evidence highlights the reduction in antibody	Thank you for your comments. This is a difficult area, and we appreciate that the evidence can be interpreted in various ways. The GDG spent a lot of time debating this issue and eventually decided that targeted use

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				titres over time but balances the increased specificity of c-peptide with time from diagnosis . However the data from publications from Hattersley (Exeter) and Owens (Oxford) using combinations of multiple pancreatic autoantibodies and urinary c-peptide (Cheap and easily obtained) suggest that there may be an opportunity to reduce the number of missed diagnosis autosomal genetic diabetes if more attention was taken to immunological and biochemical phenotyping at diagnosis. Economically if urinary c-peptide and autoantibodies are used the cost is around £15.00 -£20.00 but may help avoid misdiagnosis.	of c-peptide/auto-Ab test is the most appropriate strategy at present. The GDG considered combinations of tests, but these raise further problems - does one take any positive test as diagnostic (increasing the risk of false positives) or should one require both tests to be positive (increasing the risk of missing a diagnosis). With more experience a suitable combination may become apparent, but at present the GDG did not feel able to recommend this.
Northumbria Healthcare NHS Trust	FULL NICE	7.2.6 1.3.1	131 18	With regard to recommendation 12, the timing of structured education, we point out that clinically important benefit from DAFNE is achieved regardless of duration of diabetes (Elliott et al. Does duration of type 1 diabetes affect the outcomes of structured education?	Thank you for your comments. We have amended this recommendation as follows: 1.3.1 Offer all adults with type 1 diabetes a structured education

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				Diabetologia (2012), 55, S100). We therefore propose a minor amendment to the recommendation as follows "....at the earliest 6-12 months after diagnosis or at any future time that is clinically appropriate and suitable for the patient, regardless of duration of diabetes." This evidence could be included in the narrative on page 133 under "other considerations" paragraph 3	programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] 1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes. [new 2015]
Northumbria Healthcare NHS Trust	FULL	7.2.6	131	In their commentary the GDG recognise the heterogeneity of structured education programmes for which RCT evidence has been published, and they acknowledge the variety of emphasis placed on topics within each programme as well as the variety in skills	Thank you for your comments. There is sympathy for this view within the guideline development group, but a counter view is that other education packages are used successfully. In

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				taught. We therefore question the validity of combining the outcome results from individual education progammes for the purposes of this guideline, which dilutes the positive evidence from a clinically effective programme (DAFNE) and prevents it being recommended as a specific intervention ("other considerations", page 133). In line 14 of this narrative there appears to be an editing error and the sense is lost in a crucial part of the reasoning. We would urge the GDG to reconsider recommending DAFNE specifically as a cost effective structured education intervention as recommended by the QIPP citation on the NHS evidence database.	the absence of head-to-head comparisons the guideline development group did not feel able to recommend one unequivocally over all others, although they felt comfortable steering users towards DAFNE.
Juvenile Diabetes Research Foundation	FULL	7.2.6 13	131	Diabetes education should be an integral part of diabetes care and we support any effort to reinforce this. However, this requires healthcare professionals to be trained to understand the benefits of structured education and what is available locally for people to attend. The APPG report heard evidence that over half of general practitioners do not believe that diabetes education can change the behaviour, or improve the self-management skills, of patients, while many healthcare professionals feel it is a 'tick box exercise' or	Thank you for your comment. We agree. This is an implementation issue which has been flagged to the implementation team at NICE.

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				optional extra ('Taking Control', p.12). This is perhaps one of the biggest obstacles to people receiving diabetes education.	
NHS Greater Glasgow and Clyde	FULL	7.2.6	131	RCT data is often not representative of the effects we see in routine practice (and vice versa), yet DAFNE benefit is sustained even in routine audit of clinical practice, regardless of insulin type. The NICE GDG have not considered the DAFNE audit data as it is not RCT evidence and consequently have stopped short of recommending DAFNE as the educational intervention of choice. However, DAFNE audit data published in peer reviewed journals (more recent than the original DAFNE RCT, referenced but not included by the GDG) show sustained improvement in HbA1c of at least 0.5% and around 70% reduction in both severe hypoglycaemia and DKA. Yet in contrast this draft guideline is recommending a single basal insulin on the basis of an internally commissioned metanalysis (which does not allow for variation in education or dose adjustment behaviour) that shows an absolutely tiny benefit in HbA1c and no benefit in hypoglycaemia. This seems to be an inconsistent approach.	Thank you for your comments.. The guideline development group considered the data as set out in the linking evidence to recommendations section in the full guideline. We didn't need to look beyond RCTs to recommend DAFNE. The network meta-analysis was performed to enable us to perform a cost-effectiveness analysis on the various types of insulin, and has to be interpreted in that light. An HbA1c difference which would be small in an individual person can have major cost and clinical benefit if translated to a population over many years.

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Northumbria Healthcare NHS Trust	FULL	7.2.6	132	We would like to see the Elliott paper (ref 179) and the Hopkins paper (ref 328) linked to the statement in paragraph 6 on page 132. DAFNE audit data consistently shows huge improvements in rates of severe hypoglycaemia and as such we see no reason why DAFNE education should not be recommended for people with problematic hypoglycaemia	Thank you for your comments. We agree. We are recommending DAFNE for all adults with type 1 diabetes, therefore do not need a separate recommendation for impaired awareness of hypoglycaemia unawareness. The purpose of this section is to outline anything additional that should be done for those with impaired awareness of hypoglycaemia.
MedTech Europe	FULL	8.1	160	We would like to take this opportunity to highlight the importance of preventing as much as possible glycaemic variations, including hypoglycaemia as the most dangerous complication. We would welcome NICE to consider all medical technology options when addressing this very important point.	Thank you for your comment
A Menarini Diagnostics	FULL	8.3.1	234	We believe there is an opportunity to highlight the opportunity for people with diabetes to share their full blood glucose history direct from their meters memory using new smartphone app technology and Near Field Connectivity (NFC). This means that a person with	Thank you for your comments. This particular issue was not in the scope but we have flagged the matter to NICE's surveillance team.

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				diabetes can be closely and effectively monitored at vital times from anywhere in the world, and brings real efficiencies to patient management.	
Roche Diagnostics	Full	4.2, 4.3	55, 61	The reasons to test should include adminstering insulin safely.	Thank you for the comment. The GDG agree that the aim of self-monitoring is safety, as well as efficacy, of insulin therapy but on reviewing the text considered that it adequately covered both aims, by listing specific examples of where self-monitoring would enhance safety without being exclusive.
Association of British Clinical Diabetologists	FULL NICE	8.1.5 8.1.7 1.6.6 1.6.9	194 24	From a clinical standpoint, ABCD struggles to support a target HbA1c of ≤48mmol/mol for people with type 1 diabetes. The evidence presented acknowledges the problems associated with this target. It recognises disutility associated with such a low figure, although does not explore this fully. The economic analysis accepts that it is not possible to properly calculate the cost of such a strategy as not all individuals subjected to any particular treatment modality will reach the target, and costs will therefore be underestimated by only including those who achieve target. The	Thank you for this comment. We do not recognise the disutility of the target, as setting such targets allow people to achieve the degree of glycaemic control known to reduce risk of long term complications. We have clarified this intention in re-phrasing the recommendation for the target (NICE 1.6.6; FULL, 4.2 page 55; point 39, page 60 and page 194). Furthermore the guideline

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				subsequent discussion then suggests individualised targets and audit targets of 54 mmol/mol for centres, all of which tacitly acknowledges the problems associated with aiming for low HbA1c targets. The desirability of achieving near normoglycaemia in people with type 1 diabetes is not in dispute. However, given the importance of NICE guidance in driving audit standards, we wonder if the recommendation could be couched in other terms. The NICE documentation recommendation is very blunt and could be open to misinterpretation.	development group wanted to ensure that adults with type 1 diabetes should be supported to achieve optimal outcomes. How this is achieved is an implementation issue. We have included an audit standard because we would not want misinterpretation of the intention of the target to disincentivise people and centres achieving good outcomes.
Roche Diagnostics	FULL	8.2.5	225-227	The analysis depends to a large extend up "The frequency of SMBG against which CGM was compared in the clinical studies was uncertain and therefore an assumption had been made that this was 4 times per day". - Why CGM should lead to less QALY than SMBG 10 could be explained in further detail. Please include the ICERs in table 67.	Thank you for your comment. In the Results section we do explain that "CGM is less effective and more costly than SMBG 8 and SMBG 10 when its effectiveness in terms of HbA1c reduction was assumed to be estimated via the common comparator of SMBG 4 times". When there are multiple

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					comparators and a set cost-effectiveness threshold, cost-effectiveness results are more easily expressed in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. **For ease of computation NMB is used in this analysis to identify the optimal strategy.**
Northumbria Healthcare NHS Trust	FULL	8.1.7	194	We are unpersuaded that the published evidence (based on the DCCT) makes a strong enough case for a fixed HbA1c target of 6.5%. The GDG acknowledge the rise in the rate of severe hypoglycaemia with lower	Thank you for your comment. The guideline development group consider that treatment strategies for type 1 diabetes have improved since

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				HbA1c in the DCCT. Although improved technology and structured training have markedly reduced the risk of hypoglycaemia in those with tight blood glucose control, these tools remain either unavailable or provided inconsistently, even in specialist centres. We strongly favour that patient and clinician agree an individualised target which between 6.5 and 7.5% would be consistent with a low risk of diabetic tissue complications. Our users also express a preference for a target range, to avoid the implication of 'failure' for example in a user with an HbA1c of 6.8%	DCCT. The guideline recommends recs a number of interventions that lower HbA1c without increasing risk of hypoglycaemia. **We would reiterate that 6.5 or less is a target and have therefore included an audit standard.**
Northumbria Healthcare NHS Trust	FULL	8.2.7	229	We and our users welcome the recommendation for increased blood glucose monitoring (45 and 46) which should help users tackle the rationing of testing strips that users sometimes face.	Thank you for your comment.
Northumbria Healthcare NHS Trust	FULL NICE	8.2.7 1.6.16	229 26	Recommendation 48 is likely to encourage post-prandial testing, and given the GDG's comments on inadequate evidence to support this routine behaviour in Type 1 diabetes we question the validity of its inclusion. Sometimes users do report significant post-prandial rises in blood glucose. Where this occurs and is identified as a problem (either because patients are symptomatic and/or significant blood glucose rises are	Thank you for your comment. We therefore recommended 4 times per day as the norm. We accept the concern and agree that the evidence base for benefits of routine post-prandial testing does not exist. However, we did find

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				revealed by intermittent or continuous blood glucose monitoring), DAFNE advice remains to look first at ensuring that pre-prandial blood glucose, carbohydrate-counting skills and prandial ratios are optimised. The timing of pre-prandial insulin injections may need to be examined so that injections are given up to 30 minutes before meals. If this advice is omitted by simply giving a post-prandial target range for BG there may be missed opportunities for positive intervention, and action may be taken by the user and/or healthcare professional that is counter-productive, such as increasing prandial insulin dose when in fact changing injection site or extending the interval between injection and the start of the meal might solve the problem. If the GDG choose to retain the post-prandial target guidance we would request detail on suggested timing of post meal tests and how to achieve these proposed targets if the use of a low glycaemic index, low carbohydrate diet is not to be recommended (as in 1.4.3, 1.4.7, 1.4.8 of the NICE guideline)	evidence for improved HbA1c with more frequent testing (please see section 8.2 of the full guideline). We therefore recommended 4 as the norm (and have qualified the post-prandial glucose target by adding the qualification "if the person chooses to do it") but have included a list of circumstances where more frequent testing is of likely benefit. We have added to the recommendation that if postprandial testing is done it should take place at least 90 minutes after eating.
Roche Diagnostics	FULL	8.2.7	232	Please provide full references of clinical evidence mentioned.	Thank you for your comment. We have added references as appropriate.

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Roche Diagnostics	FULL	8.2.7	237	"The key issue for this question is whether the use of simple technological aids is clinically useful in allowing people with type 1 diabetes to better interpret and react to their blood glucose measurements. This should manifest as better (lower) HbA1c levels indicating better overall control of diabetes." This could also be indicated by lower hypoglycemia rates, reduced fear of hypoglycemia, reduced time spent in hypoglycemia.	Thank you for your comment. These outcomes were all considered. Please see table 54 in the full guideline.
A Menarini Diagnostics	FULL	8.3.6	238	The consideration of whether bolus calculation (if required) should be achieved with a specific meter or a stand alone smartphone app could make it much more clear that the bolus calculation meters use test strips that are priced far higher than other blood glucose strips (> £15 for 50 compared with <£10). Therefore the cost to the NHS over time will be much lower if the person with diabetes can monitor on their meter of choice and use a bolus calculating app if required. A further drawback to the 'specific meter' approach is that if the meter breaks then the patient loses all of their data. And apps allow automatic updates as new technologies become available, including the ability for a healthcare professional to alter important patient specific settings (such as insulin sensitivity) remotely if	Thank you for your comments. We have added a comment about potential additional cost to include consideration of meters with bolus calculators built in (please see the full guideline, page 238, economic considerations, paragraph 3 first line.) But we do not recommend a specific system in our advice.

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				required.	
Juvenile Diabetes Research Foundation	FULL	8.4.5	240 247	JDRF urges NICE to include the results of an individual patient data ("IPD") meta-analysis in its review of the clinical evidence for use of CGM in adults with type 1 diabetes. Specifically, we request that the meta-analysis by Pickup et al. be included. (Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self-monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:d3805.) This IPD meta-analysis examining the impact of real time continuous glucose monitoring compared with self-monitoring of blood glucose concludes that CGM reduces HbA1c and that reductions are greatest in those with higher baseline HbA1c and those who use CGM consistently. This IPD also indicates that CGM use reduces exposure to hypoglycaemia. IPD meta-analyses are considered the gold standard of	Thank you for your comment. We have appropriately incorporated the Pickup 2011 data into our meta-analysis and it does not change the results or our recommendation.

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				systematic reviews. Results from IPD meta-analyses are regarded as more reliable and interpretable than results from other types of systematic reviews. Because reviewers have access to raw data, IPD meta analyses allow for more detailed analyses such as subgroup analyses. For example, Pickup et al. were able to test the effect of baseline HbA1c, sensor usage, and other covariates on CGM outcomes because they utilised individual patient data. These types of analyses are not possible using aggregate or summary data from published trials – the type of approach utilised in the 2012 Cochrane Review. Because of the valuable insights offered by the IPD meta-analysis from Pickup et al., JDRF urges the Institute to include this evidence in its review and to ensure that the final Type 1 Diabetes guidelines reflect the insights offered by the IPD meta-analysis performed by Pickup et al.	
Juvenile Diabetes Research Foundation	FULL	8.4.5	240 247	JDRF notes that in October 2014, results from the SWITCH study related to quality of life, treatment satisfaction, use of medical care resources, and indirect costs were published. (Hommel E, Olsen B, Battelino T,	Thank you for your comment. This study was published after the cut-off point for literature searches. This study was a sub-analysis of the

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				et al. Impact of continuous glucose monitoring on quality of life, treatment satisfaction, and use of medical care resources: analyses from the SWITCH study. *Acta Diabetol.* 2014 Oct;51(5):845-51.) - The SWITCH study was a multicentre, randomised, crossover study in which patients with type 1 diabetes (n = 153) using continuous subcutaneous insulin infusion (CSII) were randomized to a 12 month continuous glucose monitoring sensor-On/Off or sensor-Off/On sequence (6 months each treatment), with a 4-month washout between periods. Health-related quality of life (HRQOL) in children and treatment satisfaction (TS) in adults were measured using validated questionnaires. Medical resource utilisation data were collected. In adults, TS was significantly higher in the sensor-On arm, and there were significant improvements in ratings for treatment convenience and flexibility. The incidence of severe hypoglycaemia, unscheduled visits, or diabetes-related hospitalisations did not differ significantly	SWITCH study that was included for consideration by the GDG because it was published before the final cut-of date for literature searches..

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				between the two arms though adult patients made fewer telephone consultations during the sensor-On arm. The addition of CGM to CSII resulted in better metabolic control without imposing an additional burden on the patient or increased medical resource use, and offered the potential for cost offsets.	
Northumbria Healthcare NHS Trust	FULL NICE NICE	8.2.7 1.6.15 1.6.12	229 233 25 25	Recommendation 47 omits a recommendation for target BG at bedtime and the narrative on page 233 describes the GDG's concern over the proximity of the bedtime test to the last meal. The draft guideline could be interpreted as encouraging regular testing only on waking and when a meal is taken. However this is contradicted by recommendation 44 (1.6.12) which promotes a bedtime test. The GDG acknowledge that it is routine in current clinical practice to encourage a bedtime BG test and we propose testing BG on retiring (i.e. pre bed) is an important component in	Thank you for your comments. Bedtime targets would be determined by whether or not they were in the postprandial timeframe. We agree that it is important to offer guidance. We acknowledge the success of DAFNE but there is no evidence specifically to support the DAFNE bedtime target. .

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				the challenge of reducing night time hypoglycaemia. The current DAFNE target range for bedtime BG is 6.5-8.0mmol/L, and we would strongly recommend that the GDG at least consider a minimum BG for going to bed, even if uncertain about recommending a range – for example "before bed ≥6mmol/mol"	
Medtronic	FULL	8.4.6.	248	We understand that the economic evaluation on CGM was specifically conducted on the stand-alone device, and this is referred to within the full version of the guideline. Notwithstanding, we would like to highlight the current cost-effectiveness data that has been published or presented on CGM as part of a sensor augmented pump system, as these studies have not been included in the review. Simulations using the CORE Diabetes Model show that compared to self-monitored blood glucose, reductions in HbA1c with CGM translate into important reductions in diabetes-related complications and subsequently result in CGM being cost-effective compared to self-monitored blood glucose patients with type 1 diabetes	Thank you for your comment. We looked at CGM vs. SMBG as outlined in the scope as part of the monitoring question. We believe our recommendations allow for the use of CGM in the circumstances in which you are suggesting the sensor augmented pump will be beneficial and therefore allow for this. The forthcoming NICE diagnostic assessment will give further information on the more specific

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				patients in Sweden, the Netherlands and the UK (Roze et al., 2012a,b,c). This reinforces the need for clear delineation, both within the full and short versions of the guideline, between stand-alone CGM, and CGM that is used as part of a sensor augmented insulin pump. As the clinical and cost-effectiveness of integrated CGM and sensor augmented pumps, and the benefits of the system as a whole, are being assessed within the NICE DAP (in development: http://www.nice.org.uk/guidance/indevelopment/gid-dt22), we believe that the recommendations on CGM should reflect this. It should be made clear that the recommendations on CGM are primarily applicable to stand-alone CGM, and that differentiation is made between this and CGM that is used in combination with a sensor-augment pump system in order to ensure that the advice given within the Clinical Guideline is contemporary on publication. **References** Roze S, Valentine WJ, Hanas R BC. Projection of	risk:benefit issues. All of the references you have provided were considered as part of our review, however they were conference abstracts which do not meet our inclusion criteria.

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				health economics benefits of continuous glucose monitoring versus self-monitoring of blood glucose in type 1 diabetes, in Sweden. Value in Health [Internet]. 2012a;15(4):A69. Roze S, Lynch P, Brandt A-S BC. Health economic benefits of continuous glucose monitoring (CGM) versus self-monitoring of blood glucose (SMBG) in type 1 diabetes (T1DM). 6th International Conference on Advanced Technologies and Treatment for Diabetes (ATTD), Paris, France, February 27 – March 2, 2012b [Internet]. Roze S, Lynch P CM. Projection of long term health-economic benefits of continuous glucose monitoring (CGM) versus self monitoring of blood glucose in type 1 diabetes, a UK perspective. 48th Annual EASD Meeting [Internet]. Berlin, Germany; 2012c.	
Juvenile Diabetes Research Foundation	FULL	8.4.6	248 251	JDRF notes that in December 2014, results from an analysis comparing the clinical benefits and cost-effectiveness of sensor-augmented pump therapy (CSII + CGM) and self–monitoring of plasma glucose plus	Thank you for your comment. These studies were published after the cut-off point for final literature searches, however, we have flagged this

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				continuous subcutaneous insulin infusion in people with type 1 diabetes were accepted for publication in the journal Diabetic Medicine. A copy of the publication is available electronically ahead of print. (Roze S, Saunders R, Brandt AS, de Portu S, Papo NL, Jendle, J. Health economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. *Diabet. Med*. 00, 000–000 (2015)) Roze et al. use the CORE Diabetes Model was used to simulate disease progression in a cohort of people with baseline characteristics taken from a published meta-analysis. Direct and indirect costs for 2010–2011 were calculated from a societal payer perspective, with cost-effectiveness calculated over the patient's lifetime. Discount rates of 3% per annum were applied to the costs and the clinical outcomes. Results from the model indicate that use of the sensor-augmented pump (CSII + CGM) was associated with an increase in mean discounted, quality–adjusted life expectancy of 0.76 quality–	matter to the surveillance team at NICE.

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				adjusted life years (QALYs) compared with continuous subcutaneous insulin infusion and self-monitoring of blood glucose (13.05 ± 0.12 QALYs vs 12.29 ± 0.12 QALYs, respectively). Undiscounted life expectancy increased by 1.03 years for the sensor-augmented pump (CSII + CGM) compared with continuous subcutaneous insulin infusion. In addition, the onset of complications was delayed (by a mean of 1.15 years) with use of the sensor-augmented pump (CSII + CGM). This analysis resulted in an incremental cost–effectiveness ratio of 367,571 SEK per QALY gained with the sensor-augmented pump (CSII + CGM). The additional treatment costs related to the use of the sensor-augmented pump were partially offset by the savings attributable to the reduction in diabetes-related complications and the lower frequency of self-monitoring of plasma glucose.	
Northumbria	FULL	8.4.8	252	Our users would like to point out that RCT evidence comparing CGM with SBGM may not include the facility	Thank you for your comments. In our research recommendation about

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Healthcare NHS Trust				assessment that is so important to users, for example seeing trends and speed of change data from CGM and newer flash CGM can be extremely valuable in individual cases to support self-management. There may be social situations where real time monitoring gives a massive advantage for users on a daily basis such as during exercise or in a stressful work or social situation when it is not possible or would be awkward to perform an SMBG. Users would be keen to see a research recommendation from the GDG regarding the benefits of realtime CGM and flash CGM technology meter on outcomes such as user satisfaction and quality of life in addition to biological outcomes. Could this be included?	CGM, we already suggest research into anything that gives the ability to get good control, and technologies are covered.
Northumbria Healthcare NHS Trust	FULL	9.2.1	257	In the second paragraph of the introduction, we believe there may be an editing error – should there be a final phrase ".... twice daily basal regimens are increasingly used in clinical practice"?	Thank you for your comments. We have amended the text in the full guideline to read as follows: "There is evidence that, at least in some people, neither NPH nor detemir nor glargine provide 24 hour glucose control with a once-daily injection,49,438 and because of stress laid on flexibility of basal

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					dosing in structured education programmes such as DAFNE,31,9 twice-daily basal regimens are increasingly used in clinical practice."
Association of British Healthcare Industries	FULL	9.3	343 357	**Recommendation 76. If possible, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors.** The guidance indicates that "if possible" the lowest acquisition cost needle should be used. While the full guidance may put that in to context the presentation of this guidance could erroneously lead to the acquisition cost being the most important factor in the selection of needles. This is not in the best interest of patients and could impact on their ability to control their diabetes. An assumption of commodity status is not founded, with the guideline development group recognising that needle type can have an influence on outcomes and patient experience. Prescribers following recommendations to select needles on cost alone could overlook this. More generally, recommendations to	Thank you for your comments. 1. Issues to be addressed are set out in the guideline scope 2. Our methodology considered all these factors, by critical review of the data we analysed. The methodology used in the guideline is highly robust and reflects that of both Cochrane and GRADE methodology (including the issues of blinding). We conduct critical reviews of the evidence and consider all of the factors that you mention, and so we are glad that you

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				select the lowest cost device creates a disincentive for manufacturers to continue to innovate products and services that can add significant value for patients and clinicians. We request the recommendation should be removed or modified to endorse a greater balance between all the factors that contribute to the selection of a particular needle, which we interpret as being the intention of the guideline group.	agree with our methodology. With regards to blinding, even though it may not be possible for a study to be blinded, the fact that there is lack of blinding can still lead to /introduce bias, and so the evidence has been appropriately downgraded for being at 'risk' of bias. In response to your comment about including the most recent evidence. Our literature searches are rerun 8 weeks before the guideline goes out for consultation, and so recently published study data is captured and 3. The aim of NICE guidelines is indeed to take a holistic view, and in fact the GDG consider the evidence at *both*

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					an interventional level as well as a specific product level, to evaluate where any potential benefits and harms are shown. If there are technology appraisals (TAs) in existence for any of the interventions that are looked at in the guideline, we cross-refer to the guidance given in the appraisals, and so the guideline and the TAs work hand-in-hand. 4. We have amended recommendation 1.8.4.. it now reads: After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]

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BD UK	FULL	9.3 9.3.7	343 357 354 356	Becton Dickinson (BD) would like to thank the Guideline Development Group (GDG) for the opportunity to comment on the draft guideline for the diagnosis and management of type 1 diabetes in adults. BD is a leading manufacturer of both syringes and pen needles for insulin injection devices, with considerable experience in research and education on insulin injection technique, and as such would like to provide feedback on the guideline recommendations regarding needle choice and injection technique. **75. Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. [new 2015]** While the GDG have stated that needles of different lengths should be available to patients with injection-related adverse events, they have chosen not to recommend any specific length of pen needle in the draft guideline. The GDG did find some evidence to	Thank you for your comment. We are happy to stand by our recommendation based on the relevant clinical trial evidence that we assessed in the review. Thank you for supplying these references. We have looked at these and apart from Hirsch 2012 RCT, Mckay, Gibney, and Miwa (which we included in our review), none of the other references you supplied would meet our inclusion criteria for the following reasons: • DeCornick – wrong study type (survey) • DCCT – not answer the question • Morris – wrong population (young people and children)

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				suggest that the use of shorter needles (4 mm and 5 mm) may provide some benefits over longer needles (6 mm and 8 mm), but they took the view that there was insufficient evidence to support any specific guidance. We believe, however, that patient care *would* benefit from a guideline recommendation to use pen needles <8 mm in length as there are two important clinical benefits associated with shorter needles: 1) a reduction in perceived pain and 2) a reduction in the risk of intramuscular (IM) injection. In fact, since the risk of IM injection is directly related to needle cannula length, and several studies demonstrate equivalent glycaemic control with shorter vs longer needles, we suggest it is logical that needles <8 mm be considered the preferred length of pen needle for patient use. Patients who are receiving insulin for the treatment of diabetes typically need to inject themselves 2–4 times per day in order to achieve adequate glycaemic control.[1] Correct insulin administration is crucial in the management of diabetes as it prevents the occurrence of and reduces the progression of long-term complications.[2] However, non-adherence is a common	• Peyrot, and the AADE report - wrong study type (survey) • Polansky, and Hunt – wrong population – Type 2 diabetes • Hirsch 2012 – mixed population of diabetes without giving the percentages of each type. Looked at different bevels of needles which did not meet our inclusion criteria. • Bergenstal – published after cut-off date for literature search • Hirsch 2014 – does not meet our protocol • Frid – does not meet our protocol (SC vs. IM injection) • Forum – wrong study type (recommendations, not a trial) data. • Thow – wrong population

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				problem which can contribute to poor glycaemic control, with immediate adverse consequences.[3] In a survey of over 500 patients with type 1 and type 2 diabetes, 57% of patients skipped insulin injections they knew they should take, while 20% of patients "sometimes" or "often" skipped their insulin injections.[4] Injection pain was an independent and significant risk factor for omitting insulin injections.[4] Another survey of 500 patients receiving insulin injections reported that almost 30% consider the injection of insulin to be the most difficult aspect of their diabetes care, and **47% of patients said they would be more adherent to their treatment regimen if they knew of a way to ease the pain and discomfort associated with their insulin injections.**[5] The GDG identified five studies in their literature search which directly compared outcomes between needles of different lengths. The GDG found evidence of lower injection pain with shorter vs longer needles in three out of the five studies identified in their review,[6-8] citing two of these studies in the evidence statements.[6,8] The GDG stated that the evidence was weak and	(healthy) • Vaag - – does not meet our protocol • Karhgen - wrong study type (case study) • Costs – not clinical data • Frid 2010 - wrong study type (review) We agree that blinding is difficult in such trial, but the absence of blinding still can lead to potential bias, even if it is not possible to be done. Besides this, there is still the issue of lack of allocation concealment, which is known to be one of the main drivers of overestimating the effect of an intervention. Using a mixed population is still counted as indirect evidence, because this guideline focuses on

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				insufficient to make a recommendation on needle length, however we believe that there are a number of reasons why this evidence is more robust than suggested. For instance, where GRADE assessments were performed, the quality of the studies on needle length was rated as low or very low (Appendix I, Section 1.45). Two key reasons for these ratings were the "risk of bias" as a result of a lack of blinding and concealment of allocation, and "serious indirectness" as a result of the inclusion of mixed patient populations (i.e. patients with type 1 and type 2 diabetes). Blinding patients to treatment allocation in device trials is challenging, particularly in home-use studies comparing the impact of different pen needle lengths, because patients self-administer their insulin and must see the needle that they are using. Furthermore, for the same reason, blinding such a study would not accurately reflect the preparation, anticipation and self-injection process experienced by the patient; therefore non-blinded studies are considered to be more reflective of the real world self-injection experience.[9-11] Regarding the mixed patient populations, we are not aware of any evidence to suggest that perception of pain differs	type 1 diabetes. The Mckay study was included in the evidence statements. The data from this study was not assessed in GRADE because the outcome data was narratively reported, as being 'statistically significant ' or not. And thus was not suitable for meta-analysis or GRADE. Regarding the Hirsch 2010 study data, the GDG did consider the effect size to be clinically significant for the 4mm vs. 8mm, but not for the 4mm vs. 5mm needles (as stated in the evidence statements). However we agree that this was not reflected properly in the LETR and we will amend the wording. However, the data was from a single trial, and the evidence was rated as very low or low quality and so this would not be

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				between patients with type 1 or type 2 diabetes who use insulin, meaning that the inclusion of both patient populations does not appear relevant in determining the "quality" of the studies. It is unclear why McKay, 2009, one of the studies which showed a significant benefit of shorter needles over longer needles, did not meet the criteria for GRADE assessment and therefore was not considered in the evidence review statement. Based on the comments in Table 263 of Appendix G, this study appears to be of comparable quality to Hirsch, 2010 and Miwa, 2012, which did meet the GRADE criteria. We would also like to highlight that the text in Section 9.3.7 (p354) of the draft guideline currently states, "One study (Hirsch, 2010) investigated the impact of needle size on injection site pain, and found no significant difference in injection site pain with different needle lengths (4 mm vs 5 mm vs 8 mm)." Patients were surveyed on a number of experiences during the trial, including "Least pain when inserting the needle into the skin," and the preferences for the 4 mm needle vs both	enough to change our recommendation. Additionally, pain was not the only one of our critical outcomes that the GDG based their decision-making on. HbA1c and Hypoglycaemia were other critical outcomes and the cost-effectiveness was also a major consideration. We agree that the studies may not have been designed to show statistical superiority of one needle over another, and the GDG usually take these points into consideration when making their recommendations. We have now added a sentence into the LETR to reflect this. We agree with the findings that you state from the Gibney and other studies. However cost-effectiveness,

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				the 5 mm and the 8 mm for this outcome were significant.[6] This study also demonstrated statistically significant differences in VAS pain scores between the different needle lengths. Using a comparative VAS ranging from -75 mm (much less painful) through 0 mm (equally as painful) to +75 mm (much more painful), pain scores were 23.3 mm less for the 4 mm vs the 8 mm pen needle ($p<0.001$) and 11.9 mm less for the 4 mm vs the 5 mm pen needle ($p=0.019$), both clinically meaningful differences.[6] This study also noted a significantly greater overall patient preference for the 4 mm pen needle over the 5 mm or 8 mm pen needles ($p<0.05$)[6] which has not been included in the GDG summary on patient preference in Section 9.3.7 on page 354. In addition, the evidence statement which claims that there is no difference in pen needle pain on VAS between 4 and 5 mm needles is based on a *post-hoc* analysis of a subgroup of non-obese patients (BMI <30 kg/m^2).[12] We believe that the more appropriate comparison to consider from this study would be the *a priori* comparison of all patients using 4 and 5 mm pen needles, which demonstrated significantly less pen needle pain with 4 mm needles, as noted above.[6]	and the quality of the evidence (Gibney itself was not a comparative intervention study) was also taken into consideration when making the recommendation.

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				We would also like to highlight that while the GDG concluded that none of the included studies were able to demonstrate differences in biomedical outcomes such as HbA_{1c} or hypoglycaemia rate, this would in fact be expected as all of the studies were non-inferiority or equivalence trials and were therefore not designed to demonstrate significant differences in glycaemic control or hypoglycaemia. Most were too brief to even evaluate HbA_{1c} and, with the exception of Kreugel et al, 2011, reported on fructosamine or glycated albumin levels. None of the trials included patients selected on the basis of a history of frequent hypoglycaemia and none involved the intensification of insulin regimens during the study. Hypoglycaemia episodes were recorded as adverse events in most of the trials, rather than as an efficacy outcome. Therefore, there is insufficient evidence to conclude that there is no effect of different needle length on biomedical outcomes. An additional study has been conducted, presented as an abstract at the American Diabetes Association Scientific Sessions in 2013 and recently published in	

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				the Mayo Clinic Proceedings.[13] This was a prospective, non-inferiority, cross-over study conducted in obese patients, of which 92% had type 2 diabetes, comparing a 4 mm, 32G pen needle with 8 mm and 12.7 mm needles. The primary outcome was to show equivalence in HbA_{1c} over a three month period. There was no statistical difference in HbA_{1c} between the 4 mm and each of the longer needles, although HbA_{1c} levels were approximately 0.1% *lower* with the 4 mm needle. Pain and preference were also compared; pain was significantly less as measured by VAS with 4 mm needles compared with 8 mm and 12.7 mm needles (both $p<0.05$). Preference was also significantly higher for 4 mm vs 12.7 mm needles ($p<0.05$). There was no significant difference in skin leakage between the three needle lengths. Taking all of these factors into account, and considering the role of pain in adherence to insulin injection therapy, consistent data from studies that demonstrated a reduction in pain with shorter needles is worthy of consideration within the guideline recommendation.	

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				Shorter pen needles are associated with a lower risk of intramuscular (IM) injection than longer needles. Gibney et al, 2010 reported that the estimated risk of IM injection is 0.4%, 1.8%, 5.7% and 15% with 4, 5, 6 and 8 mm needles, respectively – pooled across the four common injection sites.[14] Data are now available showing the site-specific estimated risks of IM injection with needles of different length.[15] There are large differences in the risk of IM injection by needle length, injection site (thigh 2–4X higher risk than abdomen), BMI and gender. Shorter needles have a lower risk of IM injection than longer needles at all injection sites.[15] This is important because when injected IM, insulin is absorbed at variably higher rates than when injected subcutaneously; the degree of change is largely dependent on muscle exertion or exercise, which can result in glycaemic variability and hypoglycaemia.[16-20] Hypoglycaemia represents a substantial cost to the NHS with the cost of managing moderate and severe hypoglycaemia for type 1 diabetes patients estimated to be in excess of £33 million in 2010/2011.[21] There is evidence to suggest that shorter needles	

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				provide some benefits in terms of pain perception, patient acceptability and a lower risk of intramuscular injection. While we recognise that there is some uncertainty, we feel that the evidence base is worthy of further consideration than has been captured by the current recommendation, given the potential benefits that could be realised with regards to reducing pain, improving adherence to insulin therapy and reducing the likelihood of hypoglycaemia. The draft guideline currently states that members of the GDG recognise there might be theoretical circumstances where a shorter needle option might be inappropriate, for example in individuals with obesity, due to potential risk of intradermal injection. However the evidence available indicates that the risk of intradermal injection with 4, 5 and 6 mm needles is extremely low. The above-mentioned study by Bergenstal et al, 2015 prospectively demonstrated the safety and equivalent efficacy of a 4 mm pen needle vs 8 and 12.7 mm needles in obese patients.[13] As has been identified in the draft guideline, Gibney et al, 2010 studied skin thickness in 388 patients at four different	

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				sites, concluding that skin thickness is rarely greater than 3–3.2 mm, even in obese adults.[14] This finding is supported by the studies identified in the guideline showing equivalence in outcomes with needles longer and shorter than 5 mm in length.[6,8,12] In addition, current guidance on injection technique produced by the Third Injection Technique Work Shop (TITAN) states that 4, 5 and 6 mm needles can be used by patients of any body mass index (BMI).[22] From the evidence identified in the review, there appears to be no reason why needles longer than 6 mm should be used. We therefore feel that a more appropriate recommendation would be for the use of needles <8 mm in length. Such a recommendation would be aligned with those previously published by the advisory board for the Third Injection Technique Work Shop (TITAN), which concluded that 4, 5 and 6 mm needles can be used by patients of any BMI and that there is no medical rationale for recommending the use of needles >8 mm in length.[22] Similarly, the Forum for Injection Technique (FIT) has recommended the use of shorter needles with a thinner diameter for patients in	

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				the UK.[17] **References** 1 De Coninck, C. *et al.* Results and analysis of the 2008-2009 Insulin Injection Technique Questionnaire survey. Journal of diabetes 2, 168-179, doi:10.1111/j.1753-0407.2010.00077.x (2010). 2 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The New England journal of medicine 329, 977-986, doi:10.1056/NEJM199309303291401 (1993). 3 Morris, A. D. *et al.* Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet 350, 1505-1510 (1997). 4 Peyrot, M., Rubin, R. R., Kruger, D. F. & Travis, L. B. Correlates of insulin injection omission.	

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				with diabetes. Diabetes technology & therapeutics 14, 1084-1090, doi:10.1089/dia.2012.0170 (2012). 9 Polonsky, W. H., Fisher, L., Guzman, S., Villa-Caballero, L. & Edelman, S. V. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes care 28, 2543-2545 (2005). 10 Hirsch, L., Gibney, M., Berube, J. & Manocchio, J. Impact of a modified needle tip geometry on penetration force as well as acceptability, preference, and perceived pain in subjects with diabetes. Journal of diabetes science and technology 6, 328-335 (2012). 11 Hunt, L. M., Valenzuela, M. A. & Pugh, J. A. NIDDM patients' fears and hopes about insulin therapy. The basis of patient reluctance. Diabetes care 20, 292-298 (1997). 12 Hirsch, L. J., Gibney, M. A., Li, L. & Berube, J. Glycemic control, reported pain and leakage with a 4 mm x 32 G pen needle in obese and non-obese adults with diabetes: a post hoc analysis. Current medical research and opinion	

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				21 Hex, N., Bartlett, C., Wright, D., Taylor, M. & Varley, D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabetic medicine : a journal of the British Diabetic Association 29, 855-862, doi:10.1111/j.1464-5491.2012.03698.x (2012). 22 Frid, A. *et al.* New injection recommendations for patients with diabetes. Diabetes & metabolism 36 Suppl 2, S3-18, doi:10.1016/S1262-3636(10)70002-1 (2010).	
BD UK	FULL	9.3 9.3.7	343 357 354 356	**Recommendation 76. If possible, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors.** While the GDG have acknowledged that there may be advantages associated with some pen needles over others, acquisition cost is the only factor highlighted in	**Thank you for your comments. The GDG has amended the recommendation to read as follows: "76. After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-**

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				the guideline recommendation. Such a recommendation could lead to the erroneous conclusion that, aside from cost, all pen needles are the same. Furthermore, we believe that there are other factors in addition to the acquisition cost which can determine the value of the selected pen needle. The GDG highlighted that a recommendation regarding the use of shorter needles could potentially increase the cost of care in type 1 diabetes management. The costs of diabetes treatment and medical complications in the UK in 2010/2011 were estimated as £2 billion and £7.7 billion, respectively.[1] By contrast, the GDG reported that in 2012, the prescription cost of needles required for insulin administration was only £39 million; this is 1.95% of the total cost of diabetes treatment and 0.4% of the cost of diabetes treatment and complications. It is not always the case that shorter needles are more expensive than longer needles.[2] We believe that any small additional acquisition cost is likely to be outweighed by the potential benefits associated with reducing pain and the potential impact on treatment adherence, and lowering the likelihood of intramuscular	**filled and reusable insulin pen injectors. [new 2015]".**

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				injection and the associated risk of hypoglycaemia. Selecting pen needles based only on acquisition cost can have some undesirable consequences. Reports from other European countries including Denmark, Sweden, Finland and Spain have shown that the adoption of lower cost pen needles has led to problems for patients, including injection pain, injection site wounds, bending and breakage of needles, blockages, and needles that do not properly fit insulin pens.[3-9] Similar issues are beginning to emerge in the UK as some Clinical Commissioning Groups have begun to restrict formularies to include only low cost needles. Since then BD has been receiving calls to its central phone line and posts via our social media channels from patients complaining about problems they are having once they have been switched from BD needles to other brands for cost reasons. These complaints include; needles breaking during use, painful needles, large numbers of faulty needles per box, and incompatibility between needles and pens leading to insulin leakage.[10] There is a risk that poor quality needles could lead to the incorrect amount of insulin	

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				being administered and therefore impact on glycaemic control.[3] The NHS England Action for Diabetes report states that all patients with diabetes who use insulin should be supported to use it safely,[11] therefore issues associated with the quality of lower cost needles should be considered carefully. We believe that there are other factors that should also be taken into account when selecting an appropriate pen needle, in order to achieve the best outcomes for patients and health services. These include the benefits of shorter needles,[12-16] which have been described above in our response to recommendation 75, as well as other aspects of pen needle geometry that may impact on outcomes, and the provision of additional support and services. As well as reviewing studies on needles of different lengths, the GDG included studies which investigated the impact of the thickness and tapering of needles for information only and did not consider these studies as part of the main review. However two studies reported less pain with tapered needles compared with regular	

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				needles[17,18] and two studies reported less pain with thinner needles compared with regular needles.[19,20] An additional study that was not included in the GDG review has demonstrated that needles with a sharper 5 bevel tip are also associated with significantly lower pain and greater patient preference than those with a 3 bevel tip (both $p<0.01$)[5] and, since the GDG conducted the literature searches in August 2014, a study has been published demonstrating a significant difference in insulin injection pain with a 33 gauge needle compared with a 32 gauge needle ($p=0.05$).[21] As described in our response to recommendation 75, 47% of patients reported they would be more adherent to their treatment regimen if they knew of a way to ease the pain and discomfort associated with their insulin injections.[22] Therefore, we think that all aspects of needle geometry should be taken into consideration when selecting an appropriate needle. An additional factor that has not been considered by the GDG is the added value of service and support, which is not always the same for different needle vendors. The supply chain for some manufacturers is more	

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				robust than others, particularly those with well-established European production. Some manufacturers also provide additional services that are valued by patients and clinicians and can have a positive influence on outcomes. As highlighted in our comments on recommendation 77, emerging evidence suggests that injection technique is a critical factor in optimising insulin therapy, and that improving injection technique may lead to a reduction in insulin consumption and an improvement in HbA_{1c} levels.[23] There is an ongoing unmet need for more widespread structured education for people with diabetes about good injection technique in the UK. Our company has invested substantially in this clinical area and has worked as a leading partner with the academic and clinical community in the development of our understanding of what constitutes good injection technique. This has been achieved through the support of a number of international symposia and population analyses regarding injection practice across Europe, bringing together experts from a wide range of geographical locations and raising and maintaining the awareness among healthcare professionals of the importance of injection technique.	

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				Furthermore, we have supported organisations such as the Forum for Injection Technique whose purpose is to improve this important element of patient care.[24] We recognise that it is incumbent on healthcare companies to provide evidence to support products and services. Following the emergence of data highlighting the benefits of 4 mm needles, the company is investing in a level 1 clinical trial to demonstrate this more robustly.[25] BD is also working with investigators to plan a similar study to be conducted in France. A recommendation to select pen needles based primarily on acquisition cost could lead to a general reduction in product quality that may not only cause issues for patients, as has been reported in other European countries, but may also discourage innovation and investment in the development of new products and services by manufacturers like ourselves. This would be a worrying development for any field of medicine. We would advocate the removal of this recommendation or a modification of the wording to reflect the balance of factors that contribute to the selection of a particular needle. The TITAN workshop	

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				recommends that the choice of needle should be made by the patient and their healthcare professional, taking into account physical, psychological and pharmacological factors.[26] Given the importance of patient choice, a possible wording could be derived from page 356 of the draft guideline, "the cost of a needle should be balanced against a patient's desired choice prior to a decision on long-term needle use". **References** 1 Hex, N., Bartlett, C., Wright, D., Taylor, M. & Varley, D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabetic medicine : a journal of the British Diabetic Association 29, 855-862, doi:10.1111/j.1464-5491.2012.03698.x (2012). 2 Department of Health. National Health Service England and Wales Drug Tariff. February 2015 (2015). 3 Korsbaek, M. Many people experiencing needle problems. . Danish Diabetes Association,	

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				produced with different production techniques: "thin-wall" needles compared to "regular-wall" needles: an open-label study. Diabetes technology & therapeutics 11, 523-528, doi:10.1089/dia.2009.0048 (2009). 20 Aronson, R. *et al.* Insulin pen needles: effects of extra-thin wall needle technology on preference, confidence, and other patient ratings. Clinical therapeutics 35, 923-933 e924, doi:10.1016/j.clinthera.2013.05.020 (2013). 21 Valentini, M. *et al.* Efficacy, safety and acceptability of the new pen needle 33G x 4 mm. AGO 01 study. Current medical research and opinion, 1-6, doi:10.1185/03007995.2014.993025 (2014). 22 American Association of Diabetes Educators. Injection Impact Report. Availabe at http://www.injectionimpact.com/surveyresults.html Accessed February 2015 (2008). 23 Grassi, G., Scuntero, P., Trepiccioni, R., Marubbi, F. & Strauss, K. Optimizing insulin injection technique and its effect on blood glucose control. J Clin Trans Endocrinol 1, 145-	

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BD UK	FULL	9.3 9.3.7	343 357	**Recommendation 77. Advise adults with type 1 diabetes to rotate insulin injection sites and to avoid repeated injections at the same point within sites. [new 2015]**	**Thank you. Lipohypertrophy was not prioritised by stakeholders during the scoping phase and therefore was not include in the**

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			354 356	We welcome the recommendation to advise the rotation of injections sites, which we believe is an important step in improving injection technique among people on insulin therapy. Good injection technique is important in order to minimise pain and discomfort for patients and to ensure consistency in insulin dose delivery.[1-4] It can also lead to better glucose control, which can prevent long-term complications of diabetes.[5] Injection site rotation is, however, only one element of good injection technique. Other important factors to consider include correct skin fold technique (if using longer needles), angle and duration of injection, injection site care, storage of insulin, the correct use of syringes, pens and needles, injection site, and method of lipohypertrophy detection.[5] Lipohypertrophy is a common complication of insulin injection[1,6] and injection into lipohypertrophy lesions may cause delayed or erratic insulin absorption. A study of the effect of lipohypertrophy at injection sites on insulin absorption found the mean clearance of	**scope. This matter has however been flagged to the surveillance team at NICE.**

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				insulin from lipohypertrophy sites to be significantly slower ($p<0.05$) than from the non-lipohypertrophy control sites.[7] Lipohypertrophy is fairly common, reported in >70% of patients with type I diabetes and >50% of patients with type 2 diabetes in an observational study conducted in Spain.[6] The main risk factor identified was lack of, or incorrect, injection site rotation ($p<0.0001$); needle reuse was also strongly associated with lipohypertrophy ($p<0.008$). People with confirmed lipohypertrophy consumed more insulin on average per day than those without lipohypertrophy, and the authors of this study estimated the incremental cost to the Spanish healthcare system for this excess insulin consumption at more than 122 million Euros.[6] Although this was an observational study, we consider this to be compelling evidence that correct injection site rotation is a critical factor in optimising insulin therapy. A cross-sectional, observational study conducted in China, which was recently presented at the Advanced Technologies and Treatments for Diabetes conference, reported that patients with lipohypertrophy had significantly higher daily insulin doses than patients without lipohypertrophy (0.54U/kg vs 0.41U/kg;	

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				p<0.001) and significantly greater HbA_{1c} levels (8.2% vs 7.7%; p=0.003).[8] The cost of excess insulin consumption in patients with lipohypertrophy was estimated as >$630 million per year.[9] The Injection Technique Questionnaire surveyed 4,352 insulin-injecting patients with type 1 and type 2 diabetes across 16 countries including the UK and found that large numbers of patients had deficiencies with injection technique, including incorrect site rotation and a high incidence of injection related complications.[10] The survey also found that the education provided to patients on injection technique was frequently inadequate as it was either not provided or did not cover all aspects of the technique.[10] Given the importance of injection technique in the successful administration of insulin therapy, more widespread structured education regarding injection technique for people with diabetes in the UK could make an important contribution in improving health outcomes and controlling diabetes-related costs. A study which investigated the impact of targeted and	

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				individualised training in injection technique, including a switch to the shortest insulin needle (4 mm), in patients with diabetes who had been receiving insulin therapy for more than 4 years identified a mean HbA_{1c} reduction of 0.58% ($p<0.05$) and a reduction in insulin consumption of 2 units per day across the whole cohort within 3months.[11] Although we recognise this is a prospective non-controlled study, this is a potentially important finding that supports the conclusions of Blanco et al, 2013 described above.[6] Furthermore, to demonstrate this effect more robustly, two randomised controlled studies are currently planned in the UK and France comparing outcomes and healthcare resource use in type 1 and 2 diabetes patients receiving structured education on injection technique as recommended by the TITAN workshop, compared with those receiving standard advice.[1] Even though this controlled data is not yet available, the best available evidence appears to indicate that systematically disseminating good practice in injection technique can help to improve patient outcomes and reduce costs. As a result we suggest that the wording of recommendation 77 is modified to include the provision	

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				of structured education on insulin injection technique to patients with type 1 diabetes, whilst also clearly highlighting the importance of site rotation.[1] **References** 1 Frid, A. *et al.* New injection recommendations for patients with diabetes. Diabetes & metabolism 36 Suppl 2, S3-18, doi:10.1016/S1262-3636(10)70002-1 (2010). 2 Hansen, B., Kirketerp, G., Ehlers, G., Nordentoft, E. & Hansen, G. Evidence-based clinical guidelines for injection of insulin for adults with diabetes mellitus. Available at http://www.dsr.dk/artikler/documents/english/evidence-based_clinical_guidelines_for_injection.pdf Accessed February 2015 (2006). 3 Down, S. & Kirkland, F. Injection technique in insulin therapy. Nursing times 108, 18, 20-11 (2012). 4 American Diabetes, A. Insulin administration. Diabetes care 26 Suppl 1, S121-124 (2003). 5 The Forum for Injection Technique. The First UK	

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				Injection Technique Recommendations. 2nd Edition Available at http://www.fit4diabetes.com/files/2613/3102/3031/FIT_Recommendations_Document.pdf Accessed February 2015 (2011). 6 Blanco, M., Hernandez, M. T., Strauss, K. W. & Amaya, M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes & metabolism 39, 445-453, doi:10.1016/j.diabet.2013.05.006 (2013). 7 Young, R. J., Hannan, W. J., Frier, B. M., Steel, J. M. & Duncan, L. J. Diabetic lipohypertrophy delays insulin absorption. Diabetes care 7, 479-480 (1984). 8 Hirsch, L. *et al.* Lipohypertrophy - prevalence, risk factors, and clinical characteristics of insulin-requiring patients in China. Diabetes technology & therapeutics 17 (2015). 9 Hirsch, L. *et al.* Lipohypertrophy - prevalence, risk factors and clinical characteristics of insulin-requiring patients in China. Poster presented at the 8th International Conference on Advanced Technology and Treatments for Diabetes,	

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				February 18-21 2015, Paris, France Data on file (2015). 10 De Coninck, C. *et al.* Results and analysis of the 2008-2009 Insulin Injection Technique Questionnaire survey. Journal of diabetes 2, 168-179, doi:10.1111/j.1753-0407.2010.00077.x (2010). 11 Grassi, G., Scuntero, P., Trepiccioni, R., Marubbi, F. & Strauss, K. Optimizing insulin injection technique and its effect on blood glucose control. J Clin Trans Endocrinol 1, 145-150 (2014).	
Sanofi	FULL	9.2.1.10	290	In section 9.2.1 the GDG signalled a preference for once daily insulin administration. The evidence described here does not indicate a clinically important difference between once and twice daily regimens in terms of HbA_{1c} or hypoglycaemia, and only considers the use of one type of insulin. In addition, the authors of the study assessed (Le Floch 2009), conclude that 'although some individuals may	Thank you for your comment. Section 9.2.1 covers only part of the RCT evidence that informed the recommendations. The recommendations on long-acting insulin are based on a detailed health economic analysis which includes clinical outcomes (HbA1c, hypoglycaemia) and cost

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				benefit from twice-daily dosing, the most suitable routine starting schedule for detemir in a basal-bolus regimen for type 1 diabetes is once-daily injection.' Thus the evidence does not support a conclusion that either once or twice daily insulin administration should be recommended as the preferred option for people with Type 1 diabetes. We believe that dosing frequency should be agreed between the patient and their clinician, taking into consideration their lifestyle and individual needs, and no preference should be indicated by the guideline.	considerations. Details of the analysis are reported in Appendix N.
Northumbria Healthcare NHS Trust	FULL NICE	9.2.1.11 1.7.4	291 27	DAFNE welcomes the suggestion in the draft NICE guidelines for the use of twice daily insulin levemir as the recommended insulin for people with type 1 diabetes on a basal-bolus regimen. We note however that there is no guidance given on the timing of the twice daily injections. Should the first injection be, for example, on rising or with breakfast and the second be with the evening meal or at bedtime - alternatively should the injections be spaced approximately 12 hourly but the exact time of day not matter? We appreciate there may be little evidence on which to base such a recommendation, and it may be that a schedule which fits best with an individual's daily routine is considered to be of equal or greater importance. However we feel that some statement on this matter is required for the guidance of less experienced health professionals. The history behind the current DAFNE basal regimen 'on waking and on	Thank you for your support. With regards to the timing issue, morning and bedtime was the regimen we included from the RCTs. On rising and at bedtime seems to work best for most people in practice – this is based on data from NPH insulin and applied to detemir, which has not been studied, on the basis

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				retiring' for twice daily basal NPH insulin (with a minimum 7 hour gap overnight) includes the theory that a larger overlap of basal insulin action in the morning can help to counteract the dawn phenomenon – evidence which comes from the original ITTP studies in Germany. Users often find such a regimen easier to remember than having to set reminders for injections of basal insulin during daytime or evening activities.	that (a) their duration of action is similar and (b) the need for most insulin in the early hours of the morning is likely to be best covered by this. There is no current evidence to support a 12 hourly regimen and starting from the traditional timing and changing if there seems to be a clinical indication is reasonable.
Northumbria Healthcare NHS Trust	FULL NICE	9.2.1.11 1.7.5	291 27	Recommendation 63: we welcome the GDG's recognition that users may be using basal insulin other than detemir twice daily and already achieving their glycaemic targets. This is especially likely to be the case for DAFNE users who have traditionally used NPH insulin twice daily to good effect and we would be keen to ensure that users and healthcare professionals are not induced to change regimens unless there is a clinical indication (such as failure to reach target or problems with hypoglycaemia), or the user requests it.	Thank you for your comments.
NHS Greater Glasgow	FULL	9.2.1.11	291	Recommendation 62: we feel the issue of preferred insulin has been allowed to cloud the issue of education in self-management skills. We think the NICE	Thank you for your comment. There might be some differences in methodology between the trials

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and Clyde				metanalysis of basal insulin regimens is flawed because of the varying educational input and dose adjustment behaviour between the included studies. The dose adjustment strategy is pivotal to the effectiveness of any Type 1 diabetes regimen and this point appears to have been totally neglected in the NICE analysis. In any case, the powerful effect of education in lowering HbA1c is far greater than any tiny effects of detemir over other basal insulin regimens in the NICE analysis (-0.16% compared with NPH), even if the confounding factor in the metanalysis is disregarded. We note that the NICE metanalysis shows no benefit of detemir or glargine on hypoglycaemia when the GDG excluded all non-standard regimens, yet this is the commonest reason cited for clinicians choosing to use analogues in clinical practice.	included in the NMA, which is why the analysis used a random effect model to account for the between-trial heterogeneity. However, you appear to be saying that it doesn't matter which insulin is used as long as education is given; but our analysis shows that detemir is better for HbA1c and no worse for hypoglycaemia, and the differences produce a more cost-effective outcome. The GDG believe that this is sufficiently strong reason for their recommendation.
NHS Greater Glasgow and Clyde	FULL	9.2.1.11	291	Recommendation 63: the GDG have been careful not to recommend wholesale switching of existing regimens, but we think that this too is conflicting. For an existing user of NPH the interpretation of the draft guidance can only be 'detemir must be better'; we can't imagine HCPs interpreting this any differently. If the evidence is sufficiently strong to promote only detemir for the adult	**Thank you for your comment. We believe guideline readers would follow both recommendation 62 and recommendation 63 equally, as both recommendations are of equal weight.**

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				with Type 1 diabetes, to be consistent, the guideline should surely suggest switching everybody unless the user objects. If the evidence is not sufficiently strong to do this, then choice should not be restricted at all. We would prefer the guideline to stress the benefits of a twice daily basal regimen together with structured education, and acknowledge the audit and clinical practice evidence for the effectiveness of both detemir and NPH and in many cases once daily glargine; with the additional advice that users with issues related to overnight hypoglycaemia might specifically try analogues, although it appears there is no specific evidence to support this widely held belief.	
NHS Greater Glasgow and Clyde	FULL	9.2.1.11	291	Our concerns also relate to the absence of choice in the draft Type 1 basal insulin regimen guidance. The difference between the endpoint of HbA1c for people using different basal insulin regimens is very small and hence of questionable clinical relevance. If all the users had HbA1c at or around target these variations of 0.1-0.2% would be virtually irrelevant. A once daily basal regimen (using glargine) in the context of structured	Thank you for your comment. The guideline supports the use of once daily glargine or detemir if patients express the desire to avoid an extra injection in a MDI regimen.

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				education can produce excellent overall diabetic control and the importance of personalising the insulin regimen by careful consideration of lifestyle issues and discussion with the user must not be overlooked. In its current format the basal insulin guidance in the draft type 1 diabetes update overplays the evidence from the metanalysis and underplays the importance of structured education and user choice. We refer back to our general comment (1 above), that the issues of structured education and basal insulin regimen choice are closely related and to separate them may lead to incorrect conclusions and misleading advice.	
Novo Nordisk Ltd	FULL	9.2.1.11	291	Bullet 63 - request that the wording allows for consideration of once daily insulin detemir if twice daily is not suitable before changing the patient to another insulin. This prevents an unnecessary change of insulin.	**Thank you for your comment. We have revised the recommendation which now gives the option of once daily detemir or glargine if twice-daily basal insulin injection is not acceptable to the person, or once-daily insulin glargine if insulin detemir is not tolerated. This was based on the revised economic analysis.**
Sanofi	FULL	9.2.1.1	291	Patient choice is a key focus for the National Health	Thank you for your comment. We do

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		1		Service and has further been highlighted in the Chief Executive's Five year Forward View, the NHS Mandate from the Department of Health for 2014-15 and the NHS constitution which seeks to enshrine patient rights when it comes to their treatment. Page 6 Line 5 of the draft Type 1 guideline (short version) states that "Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these." The economic and clinical evidence do not provide an appropriate rationale for the hierarchy of treatment preferences within the long-acting insulin analogue class. Therefore we would suggest that the choice of which long acting insulin might be best suited to a specific patient should be retained by the patient and their treating clinician, and there should be no stated hierarchy in the guideline within the long acting insulin analogue class.	believe the clinical and economic analysis support the hierarchy of treatment suggested by the guideline recommendation. Please see detailed analysis in the full guideline (see pages 256 – 328) which explains the rationale behind the hierarchy.

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Sanofi	FULL	9.2.1.11	293 294	It is not clear which 'studies on structured education utilising flexible insulin regimens' this point refers to as there are no references listed and no specific conclusions or data are included in the guideline. Therefore it is unclear how the recommendations regarding dosing frequency have been reached, or whether they are a true reflection of the available evidence.	Thank you for your comment. The appropriate references have been included.
Association of British Clinical Diabetologists	FULL NICE	9.2.1.11 1.7.2-4	291 293 294 27	The recommendation of the insulin regimens is over reliant on data relating to HbA1c improvement and hypoglycaemia rates. Outcome data in these areas are marginal, but more importantly, data on quality of life are lacking (and acknowledged as such). This discussion suggests that the GDG discounted such considerations on largely subjective grounds. The end result is a recommendation of insulin regimens which will not sit comfortably with many clinicians. Regarding choice of insulin regimen it is not clear why cultural rather than any other aspect of individual characteristic variance is specifically mentioned. With regard to choice of insulin regimen, it would be preferable to find a wording that encourages MDI basal	Thank you for your comment. The guideline development group can only use the data that are available. Information on quality of life from direct comparisons was not conclusive. However the economic model takes into account the quality of life associated with diabetes-related complications, which are linked with the HbA1c improvement, and events such as major hypoglycaemic events. The guideline development group also ensured that their

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				bolus as being the gold standard and preferred choice or regimen rather than 'do not offer non basal bolus'.	recommendations indicated what they believe to be the first choice insulin regimen, but also easily permit other choice if the person with type 1 diabetes finds this unacceptable.
Sanofi	FULL	9.2.1.3	271 272	The results of the NMA indicate that only insulin detemir b.d. is more effective than NPH b.d. in reducing HbA_{1c}. However the assessment of efficacy is only in comparison to NPH b.d. and there is no evidence of a difference in effectiveness between the recommended first-line treatment of detemir b.d. and any of the other insulins or insulin regimens included in the NMA (glargine o.d., detemir o.d., degludec o.d., NPH o.d., NPH (o.d. or b.d.) and detemir (o.d. or b.d.). The 95% credible intervals for the difference in the change in HbA_{1c} from baseline for all other treatments include 1. Thus the evidence does not support a conclusion that insulin detemir b.d. is the most clinically effective treatment of all those included in the NMA.	**Thank you for your comment. The analysis does show that, based on the mean treatment effect, detemir b.d. is the most clinically effective of the insulin regimens of interest in reducing HbA1c. We acknowledge that the difference between insulin detemir (twice daily) and other insulin regimens, except insulin NPH (twice daily) is not considered statistically significant when taking the credible intervals into account. This uncertainty has been clearly acknowledged in our discussion and conclusion sections in the**

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					NMA and is taken into account in the economic model which uses the distribution of the treatment effects.
Sanofi	FULL	9.2.1.3	272	Section 9.2.1.3 ranks the insulins and insulin regimens in order of their clinical effectiveness. Whilst rankings may be a useful tool in the interpretation of NMAs, they should be considered only in conjunction with both a review of the quality of the evidence and the estimates of the treatment effects and their credible intervals. The GRADE Working Group proposal for applying the GRADE tool to NMAs states: "the popular approach of treatment rankings … will result in misleading inferences when most evidence is low or very low quality, or when evidence supporting higher ranked treatments … is much lower quality than evidence supporting lower ranked treatments …. Patients and clinicians may choose a lower ranked treatment with supporting evidence they can trust over a higher ranked treatment with supporting evidence they cannot trust".	Thank you for your comment. We would like to emphasise that the NMA was conducted following the methodology recommended by the NICE decision support unit. We followed their good practice recommendations, one of which is to present treatment rankings together with their 95% credible intervals to reflect the uncertainty in the ranking. We acknowledge that there is uncertainty in the ranking, which has been clearly noted in the discussion and conclusion sections of Appendix M. We also acknowledge that the quality of the RCT evidence used in the NMA is generally low, which has

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				Overall, the quality of evidence identified in the NMA was generally assessed as being low or moderate: few recommendations were made based on high quality research evidence. As such the inferences of the ranking may be misleading and should not be accepted as the basis for such a radical recommendation. In the ranking exercise, detemir (o.d. or b.d.) was ranked first, however the credible intervals for the rankings are wide, indicating that the ranking is very uncertain. Furthermore, the rankings provided in the draft guideline are not accompanied by any assessment of their quality. In terms of the treatment effect (mean difference in HbA_{1c}) the results suggest that detemir (o.d. or b.d.) is more effective than NPH (four times daily), however there is no evidence that detemir (o.d. or b.d.) is more effective than any of the other regimens, or that any other treatments, including detemir b.d., demonstrate superiority vs. any of the other treatments included in the NMA. Therefore we do not believe the results of the NMA justify the GDG's decision either to rank the	been clearly noted in the grading of the evidence. Nevertheless, this represents the current RCT evidence available in this area that the GDG had to use to inform its recommendation. However, the final GDG decision to recommend insulin detemir (twice daily) was based mainly on the conclusions of the economic model, which takes into account quality of life and costs as well as clinical effectiveness, and not on the treatment ranking or the NMA results only.

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				insulins and insulin regimens in order of clinical effectiveness, or to recommend that insulin detemir b.d. should be used as the first-line insulin in people with Type 1 diabetes.	
Novo Nordisk Ltd	FULL	9.2.1.3	273	As per point above, it is very important to be clear on the consideration of nocturnal hypoglycaemia for long-acting insulins as the selection of randomised controlled trials for use within the network meta-analysis and then subsequent ranking of insulins can be affected considerably. This is evident in the second network based on rates of severe/major hypoglycaemic events whereby none of the treatment comparisons had a treatment effect that reached statistical significance. In such a case if nocturnal hypoglycaemia was considered then perhaps this may have yielded statistically significant results and could have supported higher ranking of long-acting insulin analogues particularly insulin degludec. Additional evidence exists on the impact of hypoglycaemic events in the UK such as Evans et al. Health and Quality of Life Outcomes, 2013. 11:90 – doi: 10.1186/1477-7525-11-90 which applies different utility values for nocturnal and diurnal hypoglycaemia.	Thank you for your comment. Our network meta analysis (NMA) did not show any beneficial effect for degludec in terms of major/severe hypoglycaemia compared to other strategies. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the

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				Please note that the dose reduction observed with insulin degludec is also not accounted for in this analyses.	evidence was graded as low quality. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. This was the case also in a sensitivity analysis where the average insulin doses from the RCTs included in the network meta-analysis were used. The study by Evans cited in your comment was not selected to inform utility parameters for reasons described in Appendix N, section N.2.2.3. The estimated difference between the disutility of nocturnal and diurnal severe hypoglycaemic event was not statistically significant and the mean difference was 0.004. Even if this value had been incorporated into the economic

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					analysis we do not believe it would have made any difference to the main conclusions. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: *"*Use other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost."
Novo Nordisk Ltd	FULL	9.2.3.1	316	It states here: *'Review question: In adults with Type 1 diabetes, what are the most effective mixed insulins (degludec-aspart versus glargine versus NPH) for optimal diabetic control?'* However insulin glargine and NPH insulin are not mixed insulins. Furthermore there are other mixed insulins that are not listed – please	Thank you for pointing out this error, which we have now amended. Although the text of the review question is indeed inaccurate, the review examined the insulins set out in Table 107.

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				correct this.	
Novo Nordisk Ltd	FULL	9.2.3.1	317	Novo Nordisk requests that 'mixed insulin's are defined to include BIAsp 30 (NovoMix® 30).	**It was already included (see Table 107) – we apologise for the error in the title to this section.**
Novo Nordisk Ltd	FULL	9.2.1.4	274	The literature review found ten published economic studies but none included insulin degludec. This possibly was due to economic modelling being focused on long-term only rather than also short-term, hence leading to the exclusion of: ➢ Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. Journal of Medical Economics. 2013; 16(12):1442-1452. This study highlights the cost-effectiveness of insulin degludec based on reduced incidence of hypoglycemia and possibility for flexibility around timing of dose administration compared to insulin glargine over a 1-year time horizon for diabetes patients. And recently published:	Thank you for your comment. Ericsson et al. 2013 has been excluded as it assesses the short term effects of hypoglycaemia event reduction (see list of excluded economic studies in Appendix L). Short term time horizon and intermediate outcomes only do not meet NICE reference case, hence the exclusion. Evans et al. 2015 has been published after the cut-off for the guideline database searches (June 2014). However, the same would apply as it examines short-term effects only.

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				➢ Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T, 2015. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with Type 1 diabetes mellitus in the UK. Journal of Medical Economics, 2015. 18(1):56-68. This short-term modelling approach accommodates the treat-to-target trial design required by regulatory bodies, and focuses on the impact of important aspects of insulin therapy such as hypoglycaemia and dosing. For patients with Type 1 diabetes who are treated with a basal-bolus insulin regimen, insulin degludec is a cost-effective treatment option compared with insulin glargine. Insulin degludec may be particularly cost-effective for sub-groups of patients, such as those suffering from recurrent nocturnal hypoglycaemia and those with impaired awareness of hypoglycaemia. Although long-term cost-effectiveness modelling is of great importance it is also necessary to consider short-term cost-effectiveness modelling that accommodates the treat to target design and allows focus on the most	

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				predominant side-effect of hypoglycaemia, which can result in an economic burden for the NHS.	
Sanofi	FULL	9.2.1.4	283 285	For the most part the model input data used in the Type 1 guideline economic evaluation are derived from literature reviews and network meta-analyses. However the insulin doses employed, which are a key driver of costs within the modelling, are not based on empirical evidence but on a simplifying assumption that all regimens use an insulin dose of 24 units per day (20 units in sensitivity analysis). It is widely acknowledged and evidenced in numerous clinical studies in Type 1 diabetes that different doses are required for different insulins to achieve equivalent therapeutic effect. Of note, higher doses of insulin detemir in a once daily regimen are required to achieve equivalent therapeutic effect to o.d. insulin glargine and the dose is even greater when insulin detemir is used twice daily. This observation is evident in both studies included in	Thank you for your comment. We have acknowledged your point and we have added some additional analyses to explore the different doses issue. In a one way sensitivity analysis, only the daily dose of detemir twice daily was changed while all the other insulin regimens were kept constant; this showed that up to an increase by 25% of the standard daily dose (24 units), detemir twice daily was still the most cost effective option. In another analysis, we estimated the average daily doses for each insulin regimen from the RCTs included in the network meta-analysis, including the studies you have quoted; also in this analysis

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				the network meta-analysis comparing insulin glargine and insulin detemir. In Heller et al (2009), patients on o.d. insulin glargine completed the study with a mean body weight of 79.32 kg and mean insulin dose of 0.33 units/kg (26.2 units/day). Insulin detemir patients (pooled o.d. and b.d. patients) completed the study with a mean body weight of 79.96kg and a mean insulin dose of 0.40 units/kg overall (32.0 units/day). This represents a 21.2% higher dose than insulin glargine for equivalent efficacy. The difference is more pronounced in patients receiving insulin detemir twice daily (the majority; 65.8% of patients), where the mean endpoint insulin dose was 0.47 Units/kg (37.6 Units/day, 42.4% higher than insulin glargine). In Renard et al (2011), body weight is not stated but both insulin detemir and insulin glargine patients had a similar baseline body mass index (24.6 ± 3.5 and 25.3 ± 3.5 respectively). At endpoint, mean insulin glargine dose was 0.28 units/kg and mean insulin detemir dose was 0.39 units/kg; 39.3% higher. When these figures were substituted for the base-case	detemir twice daily was the most cost effective option. For this reason the GDG did not believe the recommendation had to be changed. Also please note that as part of the NICE consultation process, economic models are made available to stakeholders to test their reliability only. As stated in the NICE proforma that was sent out along with the model, results calculated purely for the purpose of using alternative inputs cannot be accepted.

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				values (24 units) in the CORE Diabetes model as part of our examination of the model functioning, insulin glargine o.d. demonstrated a higher Net Monetary Benefit (NMB) than insulin detemir b.d.. Using the final study dose values from the Heller study, the deterministic NMB for o.d. insulin glargine is £205,191 vs. £203,933 for insulin detemir b.d. (difference of £1,257 in favour of o.d. insulin glargine). The probabilistic NMB is £179,587 for o.d. insulin glargine and £178,375 for insulin detemir b.d., a difference in favour of o.d. insulin glargine of £1,212. The Renard figures are more difficult to model but if it is assumed that patients were of the same endpoint bodyweight as those in the Heller study, NMB in favour of o.d. insulin glargine would be £808 and £812 for the deterministic and probabilistic analyses respectively. Alternatively, if it is assumed that patients in both arms weighed the same (BMI was evenly matched in the baseline characteristics), all NMB results using credible mean bodyweights are in favour of o.d. insulin glargine.	

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				Since the inclusion of appropriate data for insulin dose appears to change the direction of the results for the economic analysis for these two products, and challenges the current conclusion that b.d. insulin detemir is more cost effective than o.d. insulin glargine, we believe that the current economic analysis should be re-examined using empirically estimated insulin doses for all the included insulins and insulin regimens.	
Novo Nordisk Ltd	FULL	9.2.1.5	285	Nocturnal and non-severe hypoglycaemia should be considered as important clinical outcomes. Nocturnal hypoglycaemia due to the associated fear of not waking up and non-severe due its high frequency and contributing to development of impaired awareness of hypoglycaemia which is particularly important in many situations including driving. Insulin degludec shows a clear advantage over insulin glargine in terms of reducing hypoglycaemia which is reflected in the insulin degludec license (Tresiba® SPC), particularly:	Thank you for your comment. We did extract and review data on nocturnal hypoglycaemia although it was not included in the network meta-analysis (NMA) as we prioritised the two outcomes that the GDG considered to be critical outcomes: HbA1c and sever/major hypoglycaemia. Additionally, the NMA was primarily undertaken to provide the input parameters to be used in the CORE model used for the cost effectiveness analysis. The CORE model does not have a

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				• Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes. Lancet. 2012;379(9825):1489-1497 • Bode BW et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med 2013;30:1293−7. There is also real world data whereby switching to insulin degludec from either insulin glargine or insulin detemir resulted in a 90% reduction in hypoglycaemia (Evans M et al. Journal of Medical Economics,2014. doi: 10.3111/13696998.2014.975234) There is also a quality of life and economical impact associated with non-severe hypoglycaemia (including nocturnal) as highlighted by Brod et al, 2011. Value	separate input parameter for the relative treatment effect on nocturnal hypoglycaemia and therefore it was not necessary to evaluate this outcome for the economic analysis. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality. **Results from the economic analysis, which considered HbA1c reduction and severe**

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				Health;14(5):665-671	**hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. The study by Brod et al (2011) did not report any cost borne by the NHS but only out of pocket costs and productivity costs. No impact on quality of life was reported either and the GDG believe these events have a negligible impact on the health-related quality of life. For this reason, we do not believe incorporating nocturnal hypoglycaemia would have made any difference to the main conclusions of the economic analysis.**
Novo Nordisk Ltd	FULL	9.2.1.5	285	The guideline should include the evidence that the mean daily basal and total insulin doses were consistently lower (statistically significantly for one trial (Heller et al. Lancet, 2012. 379(9825):1489-1497) with	Thank you for your comment. We have acknowledged your point and we have added some additional analyses to the economic analysis

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				insulin degludec than insulin glargine at end of trial.	on long acting insulin to explore the different doses issue, including the basal and bolus doses. In a sensitivity analysis, we estimated the average daily doses for each insulin regimen from the RCTs included in the network meta-analysis; this included the total insulin dose (basal and bolus); in this analysis detemir twice daily was the most cost effective option while degludec was more costly and less effective.
Novo Nordisk Ltd	FULL	9.2.1.5	285	Insulin detemir versus insulin glargine. Novo Nordisk feel that the bullet point regarding major hypoglycaemia, should be amended to reflect the clinical evidence found in a RCT by Pieber et al 2007. In this study the risks of both severe and nocturnal hypoglycaemia were significantly lower with twice daily insulin detemir compared to once daily insulin glargine. ($p<0.05$).	Thank you for your comment. The Pieber 2007 study that you refer to was only a conference abstract, and therefore would not have been included in this review.

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Novo Nordisk Ltd	FULL	9.2.1.5	285	Real world evidence is a useful source of information to validate the evidence seen in RCTs. We would request that the following study is considered: ➢ Evans M, McEwan P, and Foos V. Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practice—a case-based evaluation. Journal of Medical Economics 2014, 1–10. Online print: 1369-6998. doi:10.3111/13696998.2014.975234.	Thank you for your comment. For intervention reviews where there is a lot of RCT evidence (which is the best study type to answer these questions), we do not look at very low level evidence such as case series studies.
Northumbria Healthcare NHS Trust	FULL	9.2.1.5	286	In the narrative description of the evidence section "Detemir vs NPH", line 14, we believe 'glargine' should read 'NPH'	Thank you for your comment. We have amended the wording.
Novo Nordisk Ltd	FULL	9.2.1.5	286	Insulin detemir versus NPH insulin. Typing error - the statement above bullet 6 in this section states *'Low and very low quality evidence showed no clinically important benefit of detemir over glargine for the following outcomes'*. We believe this relates to; insulin detemir over NPH insulin.	Thank you for your comment. We have amended the wording.

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Novo Nordisk Ltd	FULL	9.2.1.5	287	Insulin degludec versus insulin detemir. In addition to the single study by Iwamoto et al 2013, there is another RCT by Davies et al 2014. This trial assessed the efficacy and safety of insulin degludec compared with insulin detemir, both administered once daily as basal treatment in participants with Type 1 diabetes mellitus. The primary outcome was non-inferiority of insulin degludec to insulin detemir in HbA_{1c} reduction after 26 weeks. The study showed that insulin degludec administered once-daily as part of basal–bolus therapy was non-inferior to insulin detemir in lowering HbA_{1c} and is associated with a significantly lower risk of nocturnal confirmed hypoglycaemia in conjunction with a significantly larger reduction in mean FPG than basal–bolus therapy with insulin detemir. Novo Nordisk request that the results of this study should be added to the bullet points listed in this section and cited in the summary of evidence tables.	**Thank you for your comment. This study (Davies 2014) was published after our cut-off date for our final literature search.**
Novo Nordisk Ltd	FULL	9.2.2.4	311	Insulin aspart vs human insulin. Novo Nordisk request that the randomised controlled data showing a reduction in major nocturnal hypoglycaemia with aspart	Thank you for your comment. We did extract and review data on nocturnal hypoglycaemia although it

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				versus human insulin should be acknowledged here since this is an important clinical outcome for patients with Type 1 diabetes. • Insulin aspart has been shown to significantly reduce the rate of major nocturnal hypoglycaemia in a double blind cross over trial in 155 adults with Type 1 diabetes. Risk of minor hypoglycaemic events were also significantly lower with insulin aspart and there was no difference in glycaemic control observed between treatments (Heller et al. Diabetic Medicine, 2004; 21, 769-775). • Another study was carried out to investigate whether insulin aspart and insulin detemir could reduce the rate of severe hypoglycaemia in comparison with human insulins in patients with Type 1 diabetes who are at high risk of such events over 2 years. The data showed treatment with insulin detemir and insulin aspart vs. human insulin significantly reduced the rate of severe hypoglycaemia; (0.5 events /patient/year). The difference between the treatments was seemingly	was not included in the network meta-analysis (NMA) as we prioritised the two outcomes that the GDG considered to be critical outcomes: HbA1c and sever/major hypoglycaemia. Additionally, the NMA was primarily undertaken to provide the input parameters to be used in the CORE model used for the cost effectiveness analysis. The CORE model does not have a separate input parameter for the relative treatment effect on nocturnal hypoglycaemia and therefore it was not necessary to evaluate this outcome for the economic analysis. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients

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				greatest during night-time (no formal statistical analysis) (Pedersen-Bjergaard et al. Lancet Diabetes Endocrinol 2014. doi: 10.1016/S2213-8587(14)70073-7). This is important data for the subgroup of patients at high risk of hypoglycaemia and should be reflected in the guideline. It should also be added to the section on insulin detemir.	experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. The Pedersen-Bjergaard study was excluded from our review because it did not meet our inclusion criteria. Patients were given different short-acting insulins in each of the arms. In our review we required that the short-acting insulin was the same in

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					both arms, so that any effect seen for outcome measures could be attributed to the difference in long-acting insulin, rather than the short-acting insulin which would have confounded the data.
Novo Nordisk Ltd	FULL	9.2.2.5	313	It states 'No direct comparison data for the impact of aspart therapy versus human insulin therapy on the incidence of nocturnal hypoglycaemia were available.' This is not the case since there is a randomised controlled trial addressing this which demonstrates a significant reduction in major nocturnal hypoglycaemia with insulin aspart versus human insulin ((Heller et al. Diabetic Medicine, 2004; 21, 769-775) as detailed above.	**Thank you for this comment. We have amended the text as appropriate.**
Novo Nordisk Ltd	FULL	9.2.3.5	329	Novo Nordisk requests that insulin degludec should be cited here as an option for patients with nocturnal hypoglycaemia as detailed above.	Thank you for your comment. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in

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					terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: **"Use other basal insulin regimens for adults with type 1 diabetes**

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					only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets. When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost".
MedTech Europe	FULL	9.3.7	354	Recommendation 76 of the draft guideline advises use, in this case of pen needles, based on lowest acquisition cost where possible. Clearly, if all other things are equal, it is not unreasonable to make a choice based on cost. However, we believe this should not be the primary consideration where there are other important performance and value factors. For example, in the case of pen needles we believe that the recommendation erroneously makes acquisition cost the most important factor in the selection of needles, suggesting that all needles are the same. More generally, such a focus on the cost of a medical technology raises questions about the remit of NICE in developing guidelines. The objectives of a guideline include improving the quality of care of patients and assessing how well different treatments and ways of	Thank you. Needle length was a question prioritised for consideration by stakeholders, and therefore is included in the guideline. The recommendation on acquisition cost has been amended (1.8.4 in the short version) as follows: **1.8.4 After taking clinical factors into account, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]**

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				managing a specific condition work. The objectives can also include an assessment of value for money. In our view these should be intervention level assessments, for example assessing the value of insulin therapy as whole, rather than explicit judgements about individual medical technologies. It is very likely that an unqualified focus on cost such as this one will lead to a general reduction in product quality that could cause problems for patients. This is an outcome that does not appear to be what is intended by the creation of such a guideline and does not correspond with the objective to improve the quality of care. Additionally, recommendations from NICE to select the lowest cost device may discourage innovation in products and services that can add significant value.	
Lilly UK	FULL	9.3.7	354	In response to Recommendation 76: Lilly recommends the use of BD needles with all of our insulin devices. Therefore the choice of needle should be made based on individual patient needs and not on acquisition cost alone.	Thank you for your comment. We have amended the recommendation about needle choice (1.8.4 in the short version): 1.8.4 After taking clinical factors into account, choose needles with the lowest acquisition cost to use

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					with pre-filled and reusable insulin pen injectors. [new 2015]
Faculty of Pharmaceutical Medicine	FULL	11	19	Give guidance as to when the 10 times should be.	Thank you for your comment. It is not possible to do this. The potential indications for using more than 4 times daily are many, and the timing of the extra measurements will be case-dependent.
Association of British Clinical Diabetologists	FULL NICE	11.2.6 1.10.8	399 31	The evidence on treatment for impaired awareness of hypoglycaemia is reviewd. The main conclusion is that there is benefit in reviewing the basics of an individual's knowledge of diabetes and reviewing their insulin treatment and techniques. They may respond to CGM or CSII. All of this is currently the responsibility of local commissioning at CCG level. Evidence is presented suggesting that certain educational interventions are of benefit, and these may not be available locally. The recommendation is that referral to a specialist centre is considered for those wo do not respond to basic review of their insulin and education. It is not clear on what basis referral to a specialist centre is	Thank you for this comment. The recommendation does not recommend referral to a specialist centre after a "basic review of their insulin and education" – it makes no reference to "basic" and also recommends appropriate deployment of deployment of CSII and CGM. The GDG considered that if problems persisted despite all the above, referral to a specialist centre was indicated. The GDG wishes to support such referral in a timely manner to avoid adults with type 1

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				recommended. Is there evidence to show that specilist centre referrals achieve better results than local care ? It may be that availability of the dedicated hypo unawareness education courses are only provided by or via specialist centres, but this should be spelled out more clearly in the recommendations if this is the sole aim of tertiary referral.	diabetes experiencing years of problematic hypoglycaemia
Novo Nordisk Ltd	FULL	11.3.5	406	Bullet 96, Novo Nordisk request that insulin degludec should be cited as a treatment option here since it has a significantly lower risk of nocturnal hypoglycaemia in comparison to insulin glargine and has clear clinical benefits for this patient group.	Thank you for your comment. We have included nocturnal hypoglycaemia as a separate outcome in a pair-wise meta-analysis; this analysis shows that there was no clinical difference between degludec and glargine in terms of number of patients experiencing nocturnal hypoglycaemia episodes. However there was a clinically significant difference favouring degludec versus detemir for the same outcome measure. However this was from a single very small study, and the evidence was graded as low quality.

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					Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec is dominated (ie more costly and less effective) in the base case as well as all sensitivity analyses by detemir twice daily. As the CORE model does not have a separate input parameter for the relative treatment effect on nocturnal hypoglycaemia, this outcome was not separately included in the economic analysis. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: **"Use other basal insulin regimens for adults with type 1 diabetes only if the regimens in recommendations 1.7.3 and 1.7.4 do not deliver agreed targets.**

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					When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost".
Faculty of Pharmaceutical Medicine	FULL	12	7	Add a line for post-prandial targets here as well.	Thank you for your comment. We therefore recommended 4 times per day as the norm. We accept the concern and agree that the evidence base for benefits of routine post-prandial testing does not exist. However, we did find evidence for improved HbA1c with more frequent testing (please see section 8.2 of the full guideline). We therefore recommended 4 as the norm (and have qualified the post-prandial glucose target by adding the qualification "if the person chooses to do it") but have included a list of circumstances where more frequent testing is of likely benefit.

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					We have added to the recommendation that if postprandial testing is done it should take place at least 90 minutes after eating.
National Diabetes Nurse Consultant Group	FULL	12 10 20	11 24	% results should not be included Laboratories stopped reporting these results in 2011 and 1.6.3 page 23 refers to IFCC standardisation. The inclusion potential encourages practitioners to continue to convert back to % and continue to discuss results in % not mmol/mol.	Thank you for your comment. We have included % results in brackets after IFCC standardised levels because some non-specialists will still find this easier; we do not think this encourages % use. We have also used % figures when reporting the literature if this is what was how the figures are presented in the studies.
A Menarini Diagnostics	FULL	12.1.1	407	We welcome that the shortcomings of urine testing are described, however the consequence is unclear. For example, that urine tests may remain positive for 48 hours after ketogenesis and lipolysis have stopped can lead to over treatment with insulin and dangerous hypoglycaemia is not described. Also, the inability of urine testing to detect the main ketone body (beta-hydroxybuyrate) is described but the consequence of a	Urine ketone testing only features in the rec about home monitoring, where it is an option (as is a blood test). There was only one study on blood ketone testing at home, which was confounded as described in section 12.3.2. Given the substantially higher cost of blood

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				false negative test should be made much clearer to help prevent the potentially fatal but avoidable complication of DKA. Given the lack of efficacy of urine ketone testing it is disappointing that the draft guidelines still retain the practice as an option to consider. We believe this puts patients at risk.	ketone strips, the GDG did not feel able to unequivocally recommend blood over urine testing in this setting.
A Menarini Diagnostics	FULL	12.1.1	407	We welcome that the draft document outlines the benefits of blood ketone testing versus uring testing . However the opportunity to convey that sheer logic dictates that a much more reliable method of detecting ketosis in a timely way will help reduce hospitalisations and save lives seem to be lost	Thank you for your comment. Urine ketone testing only features in the recommendation about home monitoring, where it is an option (as is a blood test). There was only one study on blood ketone testing at home, which was confounded as described in section 12.3.2. Given the substantially higher cost of blood ketone strips, the GDG did not feel able to unequivocally recommend blood over urine testing in this setting.
A Menarini Diagnostics	FULL	12.3.2	417	We believe there is a clear imbalance in the way the economic considerations are explained. The unit cost of blood ketone strips is prominent, and the use of 'forty times more expensive' may dissuade use of blood	Thank you for your comment. We have amended the economic considerations which now read: "Blood ketone test strips have a

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				ketone monitoring when the patient and economic benefit should really merit it. The substantial cost savings due to reduced hospitalisations is hidden later and overeaf.	higher initial cost (£20.32 for a pack of 10) compared to urine ketone test sticks (£2.50 for a pack of 50)."
A Menarini Diagnostics	FULL	12.3.2	418	We disagree that there could be additional cost implications due to education from healthcare staff on how to test for blood ketones and interpret results. The test process and method of interpretation is entirely familiar to any person with Type 1 Diabetes as it is the same as process as blood glucose testing and the results are in the same format. This contrasts with the training required for urine testing in which results need visual interpretation and there is additional training required if a patient is to understand the clear and misleading shortcomings of urine ketone testing as described on page 407 (12.1.1)	Thank you for your comment. In the only study of home ketone monitoring, subjects were specifically trained in its use and interpretation of results, therefore the effectiveness data was based on this additional component. However we have amended the economic considerations to say that "the GDG acknowledged that there may be additional cost implications" associated with training, instead of "The GDG acknowledged that there would be additional cost implications".
Coeliac UK	FULL	13.6	425	Guidelines state that "In adults with type 1 diabetes who have a low BMI or unexplained weight loss, assess markers of coeliac disease". In order to be consistent with CG 86 on Recognition and Assessment of Coeliac	Thank you for your comment.. We have added a cross- reference to the Coeliac guideline and retained our recommendation.

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				Disease (2009) and the NICE guidelines for Diabetes in Children and Young People (update), the guidelines should state that adults with type 1 diabetes should be screened for coeliac disease at diagnosis irrespective of symptoms.	
Association of British Clinical Diabetologists	FULL	16.1	459	In the management of gastroparesis, the only interventions reviewed have been pharmacological, or with CSII. Some mention should be made of simple improvement in glycaemic control through insulin management.	Thank you for your comment. We agree with the statement and refer to this in the FULL guideline, where we discuss the importance of an accurate diagnosis and the impact of hyperglycaemia on gastric emptying (page 459, 16.1.1, para 1 lines 7-9) and the need for optimising glycaemic control (page 459, para 3, first sentence). The GDG did not find evidence of how to achieve "simple" improvement in glycaemic control in the situation of gastroparesis.
Association of British Clinical Diabetologists	FULL	16.11	533	Although psychological distress has been recognised as common in those with type 1 diabetes, the guidance has not commented on the role of a clinical psychologist within the diabetes team. This is an area of current interest and merits some comment, even if	Thank you for your comment. This topic area was not prioritised for inclusion in the update.This matter has been flagged to the NICE guideline surveillance team.

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				the conclusion is that there is no evidence of benefit.	
Diabetics with Eating Disorders	FULL	16.12.2	536	Unlike anorexia, bulimia and binge eating disorder, insulin omission is not named as a mental health condition in its own right in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Instead, insulin omission appeared in the DSM-IV subsumed under the criteria for bulimia. This reference has been built upon only slightly in the recently published DSM-5 by the additional inclusion of insulin omission under the criteria for anorexia nervosa Although another mention of insulin omission as clinically relevant is a welcome addition to the DSM-5, the position of DWED is that the failure to identify chronic insulin omission as a mental health condition in its own right is problematic. Under these diagnostic criteria, one may ask: "what is the difference between people with diabetes and anorexia and those with diabetes and bulimia?" Simply put, the answer is weight; however, determining eating disorder severity by weight is not relevant to people with type 1 diabetes who omit insulin. The measure of severity for this	Thank you for your comment. Please note that this section (16.12.2.) was not updated by this guideline development group, but is carried over from the 2004 guideline. This decision was taken following consultation with stakeholders before work began on the guideline itself. This matter has been flagged to the NICE guideline surveillance team.

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				demographic would more accurately be HbA1c. Furthermore, these diagnostic criteria propagate the idea that one simply has anorexia or bulimia with diabetes as a footnote. We know that there are diabetes-specific environmental factors that contribute to the development of diabulimia and, perhaps more importantly, that eating disorder treatment programmes that do not address the diabetes-related factors fail abjectly (Rodin et al, 1991; Smith et al, 2008; Ismail et al, 2010). Currently, individuals who are identified as omitting insulin are usually referred to their local eating disorder service. The difficulty is that eating disorder professionals are not experts in diabetes or the psychological implications of diabulimia, often seeing the problem as one of food alone rather than one of food, insulin and all the other stresses of the diabetes regimen. This leads to inappropriate use of NHS resources and, therefore, increased costs, not only in the initial ineffective treatment, but also in the costs of dealing with people with seriously uncontrolled	

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				diabetes over the long term. There is also an impact on the individuals themselves, which include failure to maintain employment, reliance on benefits, deterioration in mental wellbeing and relationships and, at its worst, death . A person with type 1 diabetes who has an eating disorder, particularly insulin omission, cannot be dealt with in isolation by an eating disorder team. What DWED has observed to be effective is the patients' DSNs being proactive in collaborating with both the individuals and their eating disorder teams to guide and educate them as to how diabetes can be managed whilst the eating disorder is being treated. A multidisciplinary approach is the only effective way to treat a person with type 1 diabetes and an eating disorder. Taken from Allan & Nash (2015) Guidelines must take this into consideration. It is really important that treatment is able to address the often diabetes specific roots of eating disorders, simply	

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				palming these patients off to ED services that do not understand insulin omission is a waste of everyone's time and money. It is imperative that those treating Diabetics with Eating Disorders take a multi-disciplinary approach. It doesn't matter if a type 1 who omits insulin is 15 stone or 7 stone in DKA the risk is the same and somebody somewhere has to start protecting us regardless of out weight.	
Medtronic	FULL	16.1.3	460 461	We feel this is a fair appraisal of the available data for gastroparesis in Type 1 diabetic patients. We agree the evidence is limited, however, we would like to highlight a meta-analysis by Chu (2012) as it contains a subgroup analysis among diabetic patients which may be informative to the guideline committee. Chu et al., (2012). 'Treatment of high-frequency gastric electrical stimulation for gastroparesis'. Journal of Gastroenterology and Hepatology 27 (2012) 1017–1026.	Thank you for your comment about the Chu meta-analysis. The subgroup data that they report was not subgroups from mixed population trials, but rather (as we did in our review) they assessed the data from the studies that reported the populations separately. If subgroup data was reported in a trial then we also assessed that separately in our review, as did they.

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				Further, the NICE IPG for Gastric Electrical Stimulation issued in 2004 (IPG 103) has been referred to within this section, however this IPG was superseded in 2014. We would like to request that the updated IPG (IPG 489) is referenced here, which does make specific reference to diabetic gastroparesis.	Thanks for highlighting the NICE IPG. We have added the cross-reference to the up-to-date IPG.
Diabetics with Eating Disorders	FULL	16.12.3	536	Since the 1980s researchers have investigated the rate of eating disorders in the Type 1 Diabetic population. Prevalence rates have varied wildly however and papers have been fraught with methodological problems. One of the main issues of contention is whether or not insulin omission for weight loss purposes is included as a feature of an eating disorder. In order to investigate these issues further it is necessary to look at how changing definitions in the Diagnostic Statistical Manual (DSM) have affected the diagnostic criteria for eating disorders and the role of insulin omission within them. The DSM III (1980) has no mention of Insulin omission in the guidelines for Eating Disorders and neither does the revised version (1987). Insulin Omission is first mentioned in the Eating	Thank you for your comment. Please note that this section (16.12.3.) was not updated by this GDG, but is carried over from the 2004 guideline. This matter has been flagged to the NICE guideline surveillance team.

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				disorders section in the DSM IV (1994) within the notes for bulimia, the same is published in the DSM IV revised (2000) 'Individuals with diabetes mellitus and bulimia nervosa may omit or reduce insulin doses in order to reduce the metabolism of food consumed during eating binges.' (p546)[i] Insulin omission may be viewed as a form of purging within the bulimia framework. In its most recent incarnation, the DSM V (May 2013) Insulin omission is included as a clinical feature of both Anorexia and Bulimia, in the clinical features of Anorexia the following is written 'Individuals with anorexia nervosa may misuse medications, such as by manipulating dosage, in order to achieve weight loss or avoid weight gain. Individuals with diabetes mellitus may omit or reduce insulin doses in order to minimize carbohydrate metabolism' (p376) And the following on Bulimia which is an exact replica of earlier revisions	

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				'Individuals with diabetes mellitus and bulimia nervosa may omit or reduce insulin doses in order to reduce the metabolism of food consumed during eating binges. (p381) The changing status of insulin omission as significant may contribute to the widely fluctuating estimates in prevalence. Some studies have reported a non-significant difference between type 1 diabetic females and their non-diabetic counterparts, some have reported a slightly elevated prevalence (please see table 1) and others have reported as much as a 4 times higher risk (Rukiye 2005). However there are further issues with methodology such as the demographics of the sample used, the diagnostic criteria applied, the scale of measurement used, control groups and self-report vs structured interviewing Please see appendix for table 1	

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Diabetics with Eating Disorders	FULL	16.12.4	536	Signs and Symptoms collated from patients and published on the dwed website www.dwed.org.uk Signs and Symptoms Recurrent episodes of DKA/ Hyperglycaemia Recurrent episodes of Hypoglycaemia High HbA1c Frequent hospitalisations for poor blood sugar control Delay in puberty or sexual maturation or irregular menses / amenorrhea Frequent trips to the Toilet Frequent episodes of thrush/ urine infections Nausea and Stomach Cramps Loss of appetite/ Eating More and Losing Weight Drinking an abnormal amount of fluids Hair loss Delayed Healing from infections/ bruises. Easy Bruising Dehydration – Dry Skin Dental Problems Blurred Vision Severe Fluctuations in weight/ Severe weight loss/Rapid weight Gain/Anorexic BMI Fractures/ Bone Weakness	**Thank you for your comment. Please note that this section (16.12.4) was not updated by this GDG, but is carried over from the 2004 guideline. This matter has been flagged to the NICE guideline surveillance team.**

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				Anaemia and other deficiencies Early onset of Diabetic Complications particularly neuropathy, retinopathy, gastroperisis & nephropathy Co – occurrence of depression, anxiety or other psychological disturbance i.e. Borderline Personality Disorder. Anxiety/ distress over being weighed at appointments Frequent Requests to switch meal plans Fear of hypoglycaemia Fear of injecting/ Extreme distress at injecting Continually requesting new meters (for the b.s. Solution) Injecting in private Insisting on having injected out of view Avoidance of Diabetes Related Health Appointments Lack of BS testing /Reluctance to test Over/ under - treating Hypoglycaemic episodes A fundamental belief that insulin makes you fat Assigning moral qualities to food (i.e. good for sugars/ bad for sugars) An encyclopaedic knowledge of the carbohydrate content of foods Persistent requests for weight loss medications	

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				If T1 is concurrent with hypothyroidism – abuse of levothyroxine Metformin abuse	
Diabetics with Eating Disorders	FULL	16.12.4	537	It is common knowledge that anorexia has the highest mortality rate of any mental illness but while the mortality rate for AN is 7 per 1000 and for type 1 Daiabetes is 2.2, combine the conditions and that mortality rate jumps to a truly depressing 34.6 per 1000 (Nielsen, Emborg &Mølbak 2002)	Thank you for your comment. Please note that this section (16.12.4) was not updated by this GDG, but is carried over from the 2004 guideline. This matter has been flagged to the NICE guideline surveillance team.
Faculty of Pharmaceutical Medicine	FULL	25	8	As 10 times a day, make clear that it should include post–prandial levels to optimize control.	Thank you for your comment. Post-prandial measurements may not be the reason more than 4 measurements per day are required. This will vary depending on the indication for increased monitoring frequency.
Faculty of Pharmaceutical Medicine	FULL	26	4	Add guidance as to how long after meals.	Thank you for your comment. We have added to the recommendation that this testing should be done at least 90 minutes after eating: **1.6.14 Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose**

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					level of 5–9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy – for guidance on plasma glucose targets in pregnancy, see the NICE guideline on diabetes in pregnancy.) [new 2015]
Newcastle Upon Tyne Hospitals NHS Foundation Trust	FULL	38 40 89	60	There is an appropriate focus on targeting HbA1c to 48 mmol/l and later in the guideline there is statement to avoid relaxing treatment targets in adults with impaired awareness of hypoglycaemia . We feel it should be clarified around the are of individualised glycaemic targets that patients with long duration diabetes with impaired hypo awareness and frail elderly patients with type 1 diabetes vigilant review of hypoglycaemia should be required and it may e necessary to consider a higher overall blood glucose target to avoid severe hypoglycaemia	**Thank you for your comment. We accept that frail elderly adults with type 1 diabetes may have a much higher risk;benefit ratio from optimised glycaemic control. The guideline specifically states that the HbA1c target is "to minimise the risk of long-term vascular complications" and encourages individual treatment targets. We would expect clinicians and patients to consider the relative importance of long term complications in the frail elderly. In the specific setting of impaired awareness of hypoglycaemia, the evidence**

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					shows that it is best treated by avoiding exposure to hypoglycaemia and not by increasing exposure to hyperglycaemia. Thus the quoted target ranges for glucose monitoring should be beneficial as there is a clear lower limit to the expected range.
Newcastle Upon Tyne Hospitals NHS Foundation Trust	FULL	56	61	Use of realtime CGM: Although there has not been time for a good evidenced based data set to yet be generated we felt that more consideration should have been given to flash blood glucose meters which are infact more aligned with CGM in the continuous measurement of interstitial fluid glucose. It is likely that they will revolutionise the quality of life for people with type 1 diabetes and therefore should be given consideration despite that lack of evidence as yet on overall HbA1c.	Thank you for your comment. The GDG share the excitement over the potential for such technologies but as you say there are no data available on which to judge them at present. We have added a comment in the full guideline (section 8.3, page 235): 'New technologies that allow the user to see not just a current value for blood glucose but also a trend for readings over the previous few hours, and which also do not require regular finger-pricking, were only just

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					being introduced at the time of writing this guideline and no evidence existed to allow for their assessment in self-management by adults with type 1 diabetes. It should be noted that these devices have therefore not been included in either this analysis, or in the following analysis of continuous glucose monitoring. Use of such technologies locally should be based on assessment of emerging evidence.' **We hope that there will soon be enough data for either a technology assessment or an update to this section of the guideline. This matter has been flagged to the NICE guideline surveillance team.**
Royal College of Physicians	FULL	56	62	It should be clearer that this does not refer to the new generation of flash blood glucose meters but rather to the equipment hitherto referred to as continuous	Thank you. We agree and have amended the full guideline. As stated in the response to 303, the GDG

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of Edinburgh				monitoring. Flash blood glucose meters are likely to revolutionise quality of life for many people with T1DM once they enter routine practice, and should be clearly noted not to be included in the current summary of evidence.	share the excitement over the potential for such technologies but as you say there are no data available on which to judge them at present. We have added a comment to the full guideline, section 8.3, page 235.) 'New technologies that allow the user to see not just a current value for blood glucose but also a trend for readings over the previous few hours, and which also do not require regular finger-pricking, were only just being introduced at the time of writing this guideline and no evidence existed to allow for their assessment in self-management by adults with type 1 diabetes. It should be noted that these devices have therefore not been included in either this analysis, or in the following analysis of continuous glucose

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					monitoring. Use of such technologies locally should be based on assessment of emerging evidence.' **We hope that there will soon be enough data for either a technology assessment or an update to this section of the guideline.**
Abertawe Bro Morgannwg University Health Board	FULL	60	General	HbA1c targets: whilst the guidance speaks to individualised targets, there is a significant focus on an HbA1c of 6.5% (48mmol/mol), which in our experience (and that of randomised clinical trials) is generally unachievable. Is the publication of this target really helping patients?	Thank you for your comment. The GDG believe that aiming for this target would be of considerable help to patients.
Royal College of Physicians of Edinburgh	FULL	61	62	The statement that "non basal bolus regimes should not be used" is too restrictive as there are patients who cannot cope with 4 injections a day but who can manage 2 injections. This should therefore be reconsidered.	**Thank you for your comment. The GDG accommodates this situation in recommendation 1.7.1.**

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Royal College of Physicians of Edinburgh	FULL	62	62	This does not accord with the experience of many people who live with T1DM. Glargine is preferable in the opinion of numerous people with T1DM, and many diabetologists, and should be reflected in the guideline.	Thank you for your comment. The recommendations in the guideline are based on evidence of clinical and cost effectiveness. Detemir twice daily was found to be more effective and cost effective than glargine in our network meta-analysis and cost-effectiveness analysis. However in a recommendation, glargine is specifically mentioned as an option where twice daily detemir is unsuitable (please see recommendation 63).
Abertawe Bro Morgannwg University Health Board	FULL	62	62	The recommendation to offer 'twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes' is at odds with our current practice and this is unlikely to be changed by the flimsy network meta-analyses presented by this NICE document. Once daily analogue basal insulin is our default starting position and we feel that patients with Type 1 diabetes support this stance.	Thank you for your comment. The recommendations in the guideline are based on evidence of clinical and cost effectiveness. Detemir twice daily was found to be more effective and cost effective than glargine in our network meta-analysis and cost-effectiveness

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					analysis. These were carried out following the methodologies recommended by the NICE decision support unit and have been reviewed by their experts. We also used the most up to date RCT evidence available in this area identified using comprehensive and rigorous search strategies. The results of the NMA provided estimates of the mean treatment effects, which represents the best available estimates from the current evidence, and showed that there is uncertainty in the insulin regimens' efficacy for both HbA1c and major/severe hypoglycaemia providing measures of this uncertainty which have been used to populate the economic model. Hence, GDG recommendation was not only based on the NMA results but primarily on the conclusions of the economic model which takes into

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					account not only clinical effectiveness, on these two outcomes, but also health-related quality of life, long term complications and costs.
Newcastle Upon Tyne Hospitals NHS Foundation Trust	FULL	62	62	The Guidelines recommend twice daily determir as the basal insulin of choice for newly diagnosed type 1 diabetes. The review has looked at a number of head to head trials of different basal insulins and have indeed appeared to conclude that there is no strong evidence for particular long acting insulins or once daily versus twice daily basal insulins either in reduction of hypoglycaemia or HbA1c. Despite the lack of strong evidence and based on one weak study the panel has then opted for an unsubstantiated bias towards one particular insulin manufacturer and while excluding a common basal insulin Glargine which is currently used to good effect with good outcome in large number of patients with type 1 diabetes . This seems to also disregard the evidence that tight glycaemic control and minimal hypoglycaemia can be achieved in many on 1 rather than 2 basal insulin injections per day . In light of	Thank you for your comment.The recommendation in favour of detemir b.d. is not based on one weak study, and certainly does not result from unsubstantiated bias. It results from a detailed network meta-analysis and economic modelling. This approach is not infallible, and the following recommendation therefore acknowledges that some patients will be better served by other options. Indeed, we specifically mandate against changing a different regimen that is delivering good control, in rec 63. Please also see our response to 282 about the inadequacy of current practice. With

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				the lack of hard evidence it would seem more appropriate to leave the choice of basal insulin up to the clinician and patient and focus on the glycaemia outcome to be achieved.	regard to clinician choice, the guideline is there to inform the clinician (and indeed the adult with type 1 diabetes) of the evidence on which we trust that choice will be made. We would like to emphasise that the NMA was conducted following the methodologies recommended by the NICE decision support unit and has been reviewed by their experts and its results have been considered carefully by the GDG. We also used the most up to date RCT evidence available in this area identified using comprehensive and rigorous search strategies. The results of the NMA provided estimates of the mean treatment effects, which represents the best available estimates from the current evidence, and showed that there is uncertainty in the insulin

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					regimens' efficacy for both HbA1c and major/severe hypoglycaemia providing measures of this uncertainty which have been used to populate the economic model. Hence, GDG recommendation was not only based on the NMA results but primarily on the conclusions of the economic model which takes into account not only clinical effectiveness, on these two outcomes, but also health-related quality of life, long term complications and costs.
Abertawe Bro Morgannwg University Health Board	FULL	63	General	We support the routine use of analogue rapid-acting insulin as part of basal-bolus therapy but are surprised that patients who opt for a BD fixed mixture regime should have to be treated with a twice-daily human mixed insulin in the first instance. The benefits of analogue rapid-acting insulins largely relate to the proximity of meal-time administration; why should	Thank you for your comment. The GDG did not find any evidence to support the use of rapid acting analogues as part of a twice daily mixed regimen and therefore could not recommend it.

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				patients who chose a BD regime be denied this?	
Association of British Clinical Diabetologists	FULL NICE	65 67 1.6.20 1.6.21	226 26	What was the basis for the costs associated with CGM ? This an area of rapidly changing technology (and cost). The newer products are likely to make the figures quoted here rapidly obsolete, perhaps even before the guidance is published. Some acknowledgement of this fact is required.	**Thank you for your comment. As explained in Appendix P, section P.2.2.4, "The cost of CGM strategy was based on the average of three of the main technologies available in the UK". In the same section we report the costs used in the analysis.**
Royal College of Physicians of Edinburgh	FULL	77	63	Attention should be drawn to the different rates of absorption between abdomen and thigh/hip.	**Thank you for your comment. The guideline recommends use of analogue insulins in MDI regimens and there is very little evidence for different absorption of these insulins from different sites, although it is commonly said that site is less important for them. Site was not raised as a question in the scope.**
Association	FULL	106	422	The guidance has not commented greatly on the	**Thank you for your comment**.

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of British Clinical Diabetologists	NICE	1.11.8	35	management of DKA.This is quite extraordinary in view of the fundamental changes recommended by the JBDS group, which are not given any mention at all. In that context, to leave the recommendation in NICE 1.11.8 as (for example 6 units/hour monitored for effect) looks ridiculous . Why has this random figure, with no explanation or justification, been left in the guidance.	**DKA was not in the scope. However the GDG did review the 2004 guidelines to ensure there were no significant anachronisms. In fact there is no RCT evidence for the benefit of the 1 unit/kg body weight per hour regimen in adults with type 1 diabetes and DKA – it originated in paediatrics as a conversion of the 6 unti dose. While the GDG do not wish to argue against the weight adjusted dose, it did not feel it had sufficient of an evidence base in adults to make the older recommendation dangerous. This matter has been flagged to the NICE guideline surveillance team.**
UK Clinical Pharmacy Association	FULL	131	General	Concerns that offering DAFNE during first 6-12 months might be when pt is in honeymoon phase (ie using small amount of insulin and not really in the throes of 'real life' for those with T1DM). They may derive more benefit a bit later when things have settled down more.	Thank you for your comment. It is always a trade-off between time to adjust to life with diabetes, and not wanting to delay too long before DAFNE, an effective intervention, is

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					employed. There is no equivalent evidence based programme for the newly-diagnosed. The GDG do recommend on-going education Wording of the recommendations has been amended: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] **1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes.**

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					[new 2015]
Royal College of Physicians of Edinburgh	FULL	138	69	This suggestion lacks evidence (for use of insulin pump in gastroparesis), and we would urge caution over this use of limited resources.	Thank you for your comment. We have used the word "consider" in this recommendation, showing that the evidence is limited. However, Sharma et al, 2011 ref 647,showed improved HbA1c and reduced hospital admissions as described in the FULL guideline, page 472, paragraph 5, with no evidence found against it, and this supports the recommendation as written.
UK Clinical Pharmacy Association	FULL	153	General	Glycaemic index diets. I think the wording is ambiguous. This diet is ok, but shouldn't be followed as a single recommendation wording should reflect this.	Thank you for your comment. We are very sorry but we do not understand the comment.
UK Clinical Pharmacy Association	FULL	194	General	Target of 48 mmol/mol might be too hard to achieve for the majority of pts and risks more troublesome hypoglycaemia - which may have a knock-on effect on driving etc. 48 might be achievable for some but perhaps unrealistic for all.	**Thank you for your comment. This is a target and it is recognised that targets may not always be achieved. Nevertheless, the recommendation is based on evidence that setting these as targets has benefit.**
UK Clinical	FULL	229	Gener	Aiming for 4-7 mmol/l at 'other times' would include	Thank you for your comment. We

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Pharmacy Association			al	bedtime – think this is too low and risks nocturnal hypoglycaemia	accept the concern but there is no evidence to support your view in patients using insulin analogues. The concern originally was driven by evidence that the evening meal non-analogue insulin would continue to be active after bedtime; and certainly fast acting analogues with the evening meal reduce the rate of nocturnal hypoglycaemia. The only evidence we have for a higher target (assuming the person is not going to bed in the post-prandial state, which many may be and would carry the higher target range) is that that the successful DAFNE programme uses a higher range for bedtime but we cannot say which part of the DAFNE curriculum in isolation leads to its success.
UK Clinical Pharmacy Association	FULL	291	General	Why are they suggesting BD detemir in the first instance? This would mean 5 daily injections, some patients manage well with OD glargine, I know of some	**Thank you for your comment. The clinical and cost effectiveness analysis shows that detemir b.d.**

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				who use BD glargine, I do not think this guideline should be so prescriptive.	**is the optimal insulin regimen. The guideline supports the use of once daily glargine or detemir if patients express the desire to avoid an extra injection in a MDI regimen (see recommendation 63 in the full guideline). In the absence of data on twice daily glargine, we are unable to recommend it, and we considered twice daily glargine not clinically relevant as it is not in common use.**
Novo Nordisk Ltd	FULL Appendix C	1.4	57	Please may we request that you clarify the rationale behind the inconsistency of hypoglycaemia outcomes when considering rapid-acting insulins and long-acting insulins as they have been noted differently? Please see below. • *Review Q: In adults with Type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?*	**Thank you for your comment. We have amended the text for consistency across the review questions.**

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				➢ *Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)* ➢ *Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)* ➢ *Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)* • *Review Q: In adults with Type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?* ➢ *Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)* In the first question are we right in assuming that *'Hypoglycaemia'* is referring to all or non-severe hypoglycaemia, and in the second question *'Hypoglycaemia'* refers to non-severe, severe and nocturnal hypoglycaemia?	

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				It is very important to be clear on the consideration of nocturnal hypoglycaemia and non-severe hypoglycaemia for long-acting insulins. Hypoglycaemia has significant detrimental effects on health-related quality of life Evans M et al. Health Qual Life Outcomes, 2013;11:90) and nocturnal is perhaps more important because of development of fear, both from a patient and a healthcare professional perspective, potentially resulting in sub-optimal insulin dose titration, along with missed or reduced insulin doses following an event (Brod M et al. Curr Med Res Opin, 2012 Dec; 28(12): 1947-58). These considerations contribute to sub-optimal glucose control, leading to an increased risk of vascular complications, which represent the main long-term economic implication of diabetes (Hex N et al. Diabet Med, 2012 Jul 29(7):855-62).	
Novo Nordisk Ltd	FULL Appendix N	2.2.2.3	456	*Cost of major hypo events.* Despite table 71 it is unclear how the resource utilisation has been calculated from Farmer et al (2012) and Leese et al	Thank you for your comment. We agree and we have changed the source of the cost of major hypo

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				(2003). The ambulance utilisation from the Farmer et al (2012) study unfortunately did not establish whether the patients experiencing hypoglycaemia were in fact diagnosed with diabetes or not. Furthermore it was not established whether the hypoglycaemia event was associated with a diabetes-related therapy or from some alternative cause such as alcohol. Regrettably, the diabetes treatments were not recorded for any of the patients during the call-outs. These deficiencies limit the observational value of this large study. From Leese et al (2003) healthcare resource utilisation is as 91% of patients use an ambulance, and upon reaching hospital 63% are treated in A&E, and 21% are hospitalised. Furthermore the study acknowledges that more severe hypoglycaemic events are treated at home or at the work-place by friends, relatives, or colleagues. Rather than referring to Farmer et al (2012) it would be more appropriate to consider Hammer et al 2009; 12(4):281-90 from which it can be ascertained that 77% of severe hypoglycaemic events are treated with	events which is now the paper by Hammer et al (2009) as you have suggested.

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				family/domestic setting and that 23% require the community/hospital setting in the UK. Please also note discrepancy in NHS resource unit costs: ➢ Department of Health. NHS reference costs 2012-2013. £230.00. Ambulance services: see and treat and convey(ASS02) ➢ Department of Health. PbR tariff information spreadsheet for 2014-2015. A&E admission £77.00 (VB09Z)	
Novo Nordisk Ltd	FULL Appendix N	2.2.2.3	457 458	*'QoL loss - major hypo events'*. It is acknowledged that the QoL default values of the CORE model have been used with the exception to that related to major hypoglycaemic events i.e. Currie et al (2006) but no explanation as to the reason for this. We would recommend a systematic review of all available evidence for utility/disutility associated with hypoglycaemic events; this should highlight a study by Evans et al in which there is UK relevant data (Evans et al, 2013 11:90 – doi: 10.1186/1477-7525-11-90)	Thank you for your comment. We have edited section N.2.2.3 of Appendix N to give the details of the systematic review conducted on the QoL value associated with major hypo events. The paper by Evans et (2013) reports values obtained with a direct elicitation method and does not take into account the frequency of the events (it is noted that the first event is associated with a higher

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					disutility). Therefore it was not our preferred source of utility data. In the same section in Appendix N we explain why the default value of -0.047 was changed ("As the survey is based on 3-month data, the utility decrement has been divided by 4 to obtain the annual utility decrement for anyone experiencing a severe hypo in a year (-0.012).) We have also clarified that this adjustment has been accepted by previous publications and TA submissions.
Novo Nordisk Ltd	FULL Appendix N	2.2.2.3	458	*'QoL loss - minor hypo event. Assumed no loss of utility'.* Minor or non-severe hypoglycaemia should be one of the outcomes due to the impact it has on patients' health-related quality of life. The frequency of non-severe hypoglycaemic events are higher than severe events and they also have an economical impact in the UK with increased SMBG testing. The publication by Brod et al. Value Health. 2011;14(5):665-71 was concerning non-severe hypoglycaemia resource	Thank you for your comment. The GDG considered the importance of minor hypo events to be relatively smaller compared to other outcomes such as severe hypo events and HbA1c level, which were prioritised. Also the study by Brod et al (2011) did not report any cost borne by the NHS but only out of pocket costs

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				utilisation. It found that 25.7% of people visited a healthcare professional following a non-severe hypoglycaemic event, and that people used 6.2 extra blood glucose tests following a non-severe event. Hence it is essential for this to be noted as part of the economics of healthcare.	and productivity costs. No impact on quality of life was reported either and the GDG believe these events have a negligible impact on the health-related quality of life.
Novo Nordisk Ltd	FULL Appendix N	4.5	481	It is quoted that *'Evidence is also sparse for the newly approved long-acting insulin, insulin degludec, which is understandable given its recent entry into the market'*, and this would be in the context of long-term economic modelling. For this reason it is reasonable to consider the alternative approach of short-term modelling as in the case of insulin degludec as this is crucial in terms of cost-effectiveness for the budget-constrained NHS and ofcourse the real-world evidence as mentioned above. This would no doubt support insulin degludec as a treatment option for certain patient populations who may benefit from it, as unfortunately Type 1 diabetes patients on the whole have not had any new drug innovations in the last 10 years….	Thank you for your comment. In our economic analyses, we follow the NICE reference case which states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. In the presence of other effectiveness data which enable us to model using a long time horizon, we do not feel we have to change the approach of our analysis.
Cheshire	General	Genera	Gener	**Screening**	Thank you. We appreciate the list of

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Diabetes Network		l	al	The preferred initial screening test for diabetes mellitus is now HbA1c in most situations (WHO, 2011). The main exceptions are: • rapid onset diabetes (including suspected type 1 diabetes and steroid-induced diabetes), as HbA1c reflects glycaemia over the preceding 2–3 months; and • anaemia, haemoglobinopathies and other diseases associated with changes in red cell turnover (e.g. malaria, drug-induced haemolysis) or glycation rates (e.g. chronic renal disease). In these situations, fasting plasma glucose remains the preferred screening test. It is also inappropriate to use HbA1c to identify gestational diabetes mellitus; an oral glucose tolerance test is required in this situation. Use of both HbA1c and fasting glucose tests together is not recommended - the diagnosis of diabetes should ideally be made using either HbA1c or blood glucose measurements. Urinalysis is not a recommended	factors that may influence HbA1c but screening for diabetes was not in our scope and we would not consider screening a useful method of seeking type 1 diabetes in adults. The WHO recommendation covers the diagnosis of non-type 1 diabetes and Diabetes UK specifically cautions that it "HbA1c is not appropriate for diagnosis of diabetes in patients of any age suspected of having Type 1 diabetes."

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				screening tool.	
Cheshire Diabetes Network	General	General	General	**Who to Screen?** General population screening is not recommended. The following high risk groups should be screened for diabetes every 3 years unless otherwise stated below. • White people aged over 40 years and people from black (including people of Afro-Caribbean origin), Asian and minority ethnic groups aged over 25 with one or more of the risk factors below: o a first degree family history of diabetes o overweight/obese/morbidly obese with a BMI of 30kg/m^2 and above o waist measurements as follows ➢ > 94cm (> 37 inches) for white and black men; ➢ > 90cm (> 35 inches) for Asian men; ➢ > 80cm (> 31.5 inches) for white, black and Asian women. • People who have ischaemic heart disease, cerebrovascular disease, peripheral vascular disease or treated hypertension. • People with established cardiovascular disease	We do not cover screening, only diagnosis when clinical suspicion exists.

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				(CVD) risk ≥ 20% over the next 10 years. • Women with polycystic ovary syndrome who have a BMI > 30 kg/m^2. • People who are taking atypical antipsychotics or other medicines known to affect glucose tolerance e.g. corticosteroids. • People who have fasting hypertriglyceridaemia (≥ 4mmol/L). Women who have had gestational diabetes but had a normal fasting plasma glucose test result at 6 weeks post partum should be screened annually.	
Cheshire Diabetes Network	General	General	General	**Interpretation of HbA1c results (WHO, 2011)** • **HbA1c ≥48 mmol/mol: indicates diabetes mellitus.** In an asymptomatic individual a repeat measurement is required to confirm the diagnosis. As HbA1c levels only change slowly, due to the red cell lifetime of approximately 120 days, it is recommended that at least 1 month should elapse before repeating the test.	**Thank you. These comments are not relevant to type 1 diabetes.**

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				• **HbA1c 42-47 mmol/mol: high risk of developing diabetes in the future.** Such individuals should receive intensive lifestyle advice and warned to report any symptoms of diabetes. Annual monitoring of HbA1c is recommended, but there is no need to repeat the measurement sooner. • **HbA1c 20-41 mmol/mol: normal.** This reference range should NOT be used as a target for optimal glycaemic control in known diabetics. Use of HbA1c for the diagnosis of diabetes precludes the need for fasting glucose measurements and glucose tolerance tests, except in the circumstances mentioned in paragraph 1 above and in pregnancy, but an HbA1c <48 mmol/mol does NOT exclude diabetes when/if diagnosed using glucose tests. **Interpretation of Glucose results (WHO, 2000):** As before **Procedure for OGTT:** As before	

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				Interpretation of OGTT (WHO, 2000): As before	
Royal College of Physicians	General	General	General	Endorse Association of British Clinical Diabetologists comments	Thank you.
Department of Health	General	General	General	No comments	Thank you
Heart UK	General	General	General	No comments	**Thank you**
NHS Choices	General	General	General	No comments	Thank you
Roche Diagnostics	General	General	General	**References** Barnard K, P. C., Young A, Ashraf M (2011). "Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in T1DM patients treated with multiple daily insulin injections." Diabetes Sci Technol(6): 144-149. Bode, B. W., H. T. Sabbah, T. M. Gross, L. P. Fredrickson and P. C. Davidson (2002). "Diabetes management in the new millennium using insulin pump therapy." Diabetes Metab Res Rev **18 Suppl 1**: S14-20. Cavan, D. A., R. Ziegler, I. Cranston, K. Barnard, C. G.	Thank you

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				Parkin, W. Koehler, B. Petersen, I. Vesper, M. A. Schweitzer and R. S. Wagner (2013). "Use of an automated bolus advisor improves multiple outcomes in patients treated with multiple daily insulin injections: results from ABACUS." Diabetologia **56**: S425-S425. Cavan, D. A., R. Ziegler, I. Cranston, K. Barnard, J. Ryder, C. Vogel, C. G. Parkin, W. Koehler, I. Vesper, B. Petersen, M. A. Schweitzer and R. S. Wagner (2014). "Use of an insulin bolus advisor facilitates earlier and more frequent changes in insulin therapy parameters in suboptimally controlled patients with diabetes treated with multiple daily insulin injection therapy: results of the ABACUS trial." Diabetes Technol Ther **16**(5): 310-316. Cavan, D. A., R. Ziegler, I. Cranston, K. Barnard, J. Ryder, C. Vogel, C. G. Parkin, B. Petersen, M. Schweitzer and R. S. Wagner (2013). "Use of an automated bolus advisor improves glycaemic control without increased hypoglycaemia in patients with poorly controlled Type 1 and Type 2 diabetes treated with multiple daily insulin injection (MDI) therapy: first results from the Automated Bolus Advisor Control and Utility Study (ABACUS)." Diabetic Medicine **30**: 156-156.	

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				Enander, R., C. Gundevall, A. Stromgren, J. Chaplin and R. Hanas (2012). "Carbohydrate counting with a bolus calculator improves post-prandial blood glucose levels in children and adolescents with type 1 diabetes using insulin pumps." Pediatr Diabetes **13**(7): 545-551. International Diabetes Federation (2011). "2011 Guideline for Management of PostMeal Glucose in Diabetes." Klupa, T., T. Benbenek-Klupa, M. Malecki, M. Szalecki and J. Sieradzki (2008). "Clinical usefulness of a bolus calculator in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with continuous subcutaneous insulin infusion." J Int Med Res **36**(5): 1112-1116. Langendam, M., Y. M. Luijf, L. Hooft, J. H. Devries, A. H. Mudde and R. J. Scholten (2012). "Continuous glucose monitoring systems for type 1 diabetes mellitus." Cochrane Database Syst Rev **1**: CD008101. McCulloch DK, N. D., Jean E Mulder JE "The adult patient with brittle diabetes mellitus." Pickup, J. C., S. C. Freeman and A. J. Sutton (2011). "Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self	

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				monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data." BMJ **343**: d3805. Ryder, J., D. A. Cavan, R. Ziegler, I. Cranston, K. Barnard, C. Vogel, W. Koehler, B. Petersen, I. Vesper, K. Friedman, M. A. Schweitzer and R. S. Wagner (2013). "Use of an automated bolus advisor may improve carbohydrate counting competence in patients treated with multiple daily insulin injection therapy: results from ABACUS." Diabetologia **56**: S425-S425. Samann, A., I. Muhlhauser, R. Bender, C. Kloos and U. A. Muller (2005). "Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study." Diabetologia **48**(10): 1965-1970. Schmidt, S., M. Meldgaard, N. Serifovski, C. Storm, T. M. Christensen, B. Gade-Rasmussen and K. Norgaard (2012). "Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study." Diabetes Care **35**(5): 984-990. Schütt, M., W. Kern, U. Krause, P. Busch, A. Dapp, R.	

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				Grziwotz, I. Mayer, J. Rosenbauer, C. Wagner, A. Zimmermann, W. Kerner and R. W. Holl (2006). "Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria." Exp Clin Endocrinol Diabetes **114**(7): 384-388. Ziegler, R., D. A. Cavan, I. Cranston, K. Barnard, J. Ryder, C. Vogel, C. G. Parkin, W. Koehler, I. Vesper, B. Petersen, M. A. Schweitzer and R. S. Wagner (2013). "Use of an Insulin Bolus Advisor Improves Glycemic Control in Multiple Daily Insulin Injection (MDI) Therapy Patients With Suboptimal Glycemic Control First results from the ABACUS trial." Diabetes Care **36**(11): 3613-3619. Ziegler, R., C. Rees, N. Jacobs, C. G. Parkin, M. R. Lyden, B. Petersen and R. S. Wagner (2014). "Does frequent use of an automated bolus advisor improve glycaemic control in pediatric patients treated with insulin pump therapy? First results of the BABE study." Diabetologia **57**: S417-S417. Zisser, H., R. Wagner, S. Pleus, C. Haug, N. Jendrike, C. Parkin, M. Schweitzer and G. Freckmann (2010).	

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				"Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison." Diabetes Technol Ther **12**(12): 955-961.	
Roche Diagnostics	General	4.3	62	Patients with continued hyperglycemia could also benefit from CGM: Patients not achieving adequate glycemic control using SMBG and MDI or CSII: The study by Lynch et al. (Lynch P, Attvall S, Persson S, Barsoe C, Gerdtham U. Routine use of personal continuous glucose monitoring system with insulin pump in Sweden. Diabetologia 2012; 55:432.) shows a significant reduction in HbA1c in real-life use of CGM, whilst the frequency of severe hypoglycaemic events was slightly but significantly reduced (medical records: 0.10 vs. 0.02 events/month in 6 months before and after CGM start, respectively, p=0.0021). CGM should also be available for the treatment of brittle diabetes (McCulloch DK). Other reasons may include: • High levels of physical activity (for example, sport at a regional, national or international	Thank you for your comment. We have appropriately incorporated the Pickup 2011 data into our meta-analysis and it does not change the results or our recommendation. Lynch is a pump study; pumps are not in the scope. This matter has been flagged to the NICE guideline surveillance team.

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				level), • comorbidities (for example, anorexia nervosa) or • receiving treatments (for example corticosteroids) that can make blood glucose control difficult. Patients with a baseline HbA1c of 10.0% (86 mmol/mol), for example, can expect about a 0.9% HbA1c improvement with continuous glucose monitoring when used daily, and reduced exposure to hypoglycaemia (Pickup, Freeman et al. 2011).	
Roche Diagnostics	General	8.2.6	228	"As depicted in Fig. 1, the effect of a more frequent SMBG on HbA1c-reduction was more pronounced in patients on intensified conventional (≥ 4 daily injections) or continuous subcutaneous insulin infusion therapy (HbA1c-reduction of 0.32% for one additional measurement/day) compared to patients on conventional (1–3 daily injections) therapy (HbA1c-reduction of 0.16% for one additional measurement/day)." (Schütt, Kern et al. 2006)	Thank you for your comment.. Your data supports recommendation 16.1.3 in the context that the guideline does not recommending management of type 1 diabetes in adults by 3 or less injections per day.

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				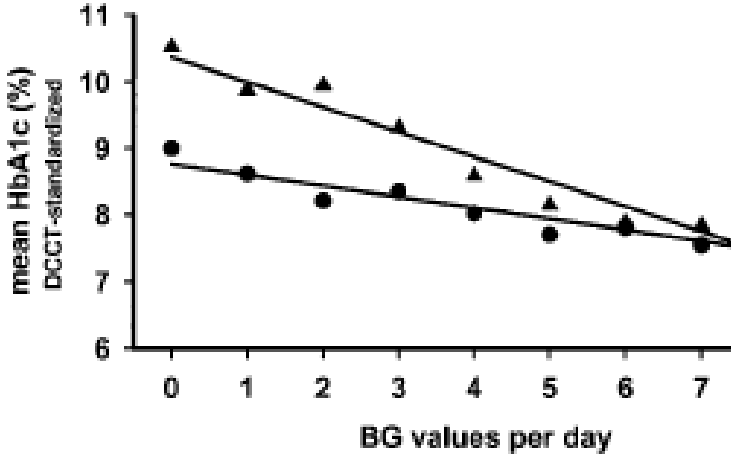 **Figure** 1: Effects of self-monitoring of blood glucose in type 1 and type 2 diabetes. (Schütt, Kern et al. 2006)	
Successful Diabetes	NICE	General	General	Attention to language throughout: some is at odds with the espoused 'person centred' philosophy on page 6. For example, the word patient does not indicate a partnership or collaborative approach but is used throughout. A further issue is that of judgmental	Thank you for your comment. The NICE editor has thoroughly edited the text to ensure it is in line with NICE's agreed style. This matter has been flagged to the NICE editorial

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				language, for example 'fail to achieve'. On page 49 and the suggestion that personal expertise on page 40 only applies to their diabetes management. Suggest that negative connotations are reversed into positive ones. For example, other ways of being positive might include 'have not yet achieved', 'have chosen different targets' or 'living with diabetes'. Please see reference 1. below for published guidance on inclusive and supportive language in diabetes.	team.
Successful Diabetes	NICE	General	General	There is very little mention of the emotional impact of being diagnosed and living with diabetes. Mention is rightly made of formal psychological and psychiatric support that may be needed, but this does not do justice to the evidence that an 'everyday' or 'empathic willingness' (ref 7 below) approach, which recognises and acknowledges emotional issues in relation to being diagnosed, is effective. Evidence 2 -7 below show that this is important and can be practically implemented to good effect and impact. May I suggest that it is acknowledged in the guidelines as currently this is a major omission of a body of relevant and important evidence.	Thank you for your comment. The guideline development group did not search for evidence on this topic and are therefore unable to make any recommendation about it. We have added the following text to the patient introduction to the full guideline, to highlight the importance of emotional support: Emotional and psychological support, both at initial diagnosis and on a continuing basis, will enhance

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					the patient's ability to live with diabetes.
Successful Diabetes	NICE	General	General	Evidence to support above: number relates to the numbers noted in the comments above. 1. Diabetes Australia 'A new Language for diabetes' position statement. July 2011. 2. Dietrich U. Factors affecting the attitudes held by women with Type 2 diabetes: a qualitiative study. Patient educ couns 1996 29(2) 13-23 3. Polonsky, W et al. Are patients' initial experiences at diagnosis, associated with attitudes and self-management over time? Diabetes Educ 2010 36 (5) 828-34 4.Levinson, W. et al. A study of patient clues and physician responses in primary care and surgical settings' JAMA, 2000, 284, 1021-1027 5. Shaban, C. et al. The role of psychological assessment in patients with newsly diagnosed Type 1 diabetes. Diabetic Med 2002; 19 (suppl 2) 98 6. Jones, A., Vallis, M., Pouwer, F. If it does not significantly change HbA1c levels, why should we waste time on it? A plea for the prioritisation of	Thank you for your comment.. We agree with the sentiment, but psychological support during diagnosis was not an area prioritised for this version of the guideline during the lengthy scoping process, and we cannot add this evidence at this stage.

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				psychsological well-being in people with diabetes. Diabetic Med, 32, 155-163 (2015) 7. Nash, J. Dealing with the diagnosis of diabetes. Practical Diabetes, 32, 1, 19-23, 2015	
Faculty of Pharmaceutical Medicine	NICE	General	General	In order to avoid ambiguity, recommend a page to list abbreviations such as "BMI"	Thank you for your comment. As BMI is a widely used and understood abbreviation, NICE do not consider it needs to be spelled out in full. **It is included in the glossary of the full guideline.**
Diabetes UK	NICE	General	General	We suggest NICE include the need for regular dental check- ups and appropriate dental care in this guideline. This is clearly explained in the draft guideline for children and young people with diabetes. This recommendation should be replicated for adults.	Thank you. Dental care was not in our scope. This matter has been flagged to the NICE guideline surveillance team.
Diabetes UK	NICE	General	General	We suggest NICE include a warning in the guideline for people with Type 1 diabetes about the dangers of substance abuse (may destabilise glucose control).	**Thank you for your comment. We have not looked at evidence around activities that might destabilise diabetes (there will be many other candidates) because this was not identified as a**

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					priority at scoping. We therefore cannot make this recommendation. This matter has been flagged to the NICE guideline surveillance team.
Diabetes UK	NICE	General	General	Throughout the guidance there is a lack of consideration of the particular difficulties faced by people with very long duration of Type 1 diabetes in setting targets and particularly in avoiding hypoglycaemia.	**Thank you for your comment.. Diabetes of all durations was discussed and considered throughout guideline development group deliberations including input form patient members.**
Novo Nordisk Ltd	NICE FULL	general	general	The most important goal in terms of treatment for people with Type 1 diabetes is to reduce HbA_{1c} to target levels, ensuring minimal risk of hypoglycaemia, and to prevent long-term micro- and macro-vascular complications. The clinical guidelines are of utmost importance not only for the UK but also internationally and so having a world-wide impact in terms of diabetes care. For this reason it is essential that the recommendations are based on robust evidence, preferably randomised controlled trials and both short-term and long-term economic modelling approaches,	Thank you for your support of the guideline.

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				and where necessary real-world evidence also be considered, to better inform decision makers ultimately for the benefit of the patient. In our response we commend your efforts, in particular recognising licensed indications, and also highlight some areas which in our opinion still need attention in order for the guidelines to be recognised as highly evidence-based and up-to-date.	
Northumbria Healthcare NHS Trust	NICE	General	11	Line 26 : before, during and after sport	Thank you for your comment. We could not find the text at the location specified; we think it relates to the recommendation about frequency of SMBG (1.6.11 in the NICE guideline) and are asking for the bullet point 'before and after sport' to be changed to 'before, during and after sport'. We have therefore amended the recommendation to read as follows: "1.6.11 Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a

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					day if any of the following apply: • the target for blood glucose control, measured by HbA1c level (see recommendation 1.6.6), is not achieved • the frequency of hypoglycaemic episodes increases • there is a legal requirement to do so (such as before driving, in line with the Driver and Vehicle Licensing Agency [DVLA] At a glance guide to the current medical standards of fitness to drive) • during periods of illness • before, during and after sport • when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy) • if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of

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					hypoglycaemia, high-risk activities). [new 2015]"
INPUT Patient Advocacy	NICE	General	11 12	Some frequent problems could be addressed if the following points were included in the key priorities: ISO 15197:2013 becomes mandatory at the end of May 2016; in the meantime, clinicians should encourage patients to use ISO compliant SMBG meters in order to ensure best available accuracy of results. Structured education should also be offered to those who have been diagnosed longer than 12 months (see point 2 below) especially if their HbA1c is above target.	Thank you for your comments. NICE guidance assumes that devices are of appropriate standard, properly maintained, and used by those trained to use them. The education recommendation text has been amended: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] 1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is

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					clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes. [new 2015]
Northumbria Healthcare NHS Trust	NICE	General	61	Column 1 row 4 "The term A1c can be sued for simplicity" should read "used"	Thank you. We have corrected this.
Successful Diabetes	NICE	1	4	Line 12 – add 'glycaemic' before 'target', as it seems to relate solely to this aspect of control	**Thank you for your comment. We have not added 'glycaemic', as this refers not just to glucose control.**
Successful Diabetes	NICE	1	6	Line 8: consider replacing 'partnership' with 'collaboration' as it better describes the relationship	Thank you for your comment. This is NICE standard text which we are unable to change. We have flagged this matter to the NICE editorial team.
Abbott Diabetes Care	NICE	1.14	38	In order to improve upon the findings within the National Diabetes inpatient audits, audit of local protocol with regard to follow up blood glucose measurement after a low glucose measurement (<3.9mmol/L) would be a positive addition to this recommendation to ensure	**Thank you for your comment. Local protocols are not within the remit of NICE guidelines.**

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				protocol implementation and to support patient safety.	
Royal College of Physicians of Edinburgh	NICE	1.11.1	34	Ketone testing should be offered routinely to all women with type 1 diabetes (TIDM) during pregnancy to minimise the risk of foetal loss secondary to normoglycaemic ketoacidosis.	Thank you. We have passed your comment to the diabetes in pregnancy guideline team.
Abbott Diabetes Care	NICE	1.11.1	34	We welcome the addition of blood ketone testing to the NICE guidelines and reiterate the evidence of its superiority over urine glucose testing therefore suggesting that blood ketone is routinely offered over urine testing.	**Thank you.**
Diabetes UK	NICE	1.11.1	34	The word "consider" should be removed from this point as all people with Type 1 diabetes should have some form of ketone measurement to help prevent DKA.	Thank you for your comment. We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and

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					preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient. .
Successful Diabetes	NICE	1.10.12	33	Line 9: add 'emotional and' before 'psychological problems'	Thank you for your comment. The GDG consider that 'emotional' is included in 'psychological', and we feel that the term 'psychological' is preferable to 'mental health / psychiatric' which is the newer NICE terminology so this has not been changed.
Dexcom	NICE	1.10.13	33	CGM should be considered to be used with nocturnal hypoglycaemia. It is unrealistic to assume a T1 patient will awake multiple times every night to perform SMBG	Thank you for your comment.. This recommendation is about managing nocturnal hypoglycaemia, not detecting it.
Medtronic	NICE	1.10.13	33	As per comment 7 on the Full guideline	Thank you for your comment.. The recommendation is 1.6.3. We have amended it to: "*Use methods to measure HbA1c that have been*

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					calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation. [new 2015]"
Abbott Diabetes Care	NICE	1.11.12	35	We recommend that in order to support this, blood ketone testing is also considered within a formal	Thank you for your comment. The comment we have received appears to be incomplete so we have answered as best we can. **This recommendation does not preclude the use of ketone monitoring – it is aimed at ensuring close monitoring of all aspects, not specifying exactly what should be monitored**
Faculty of Pharmaceutical Medicine	NICE	1.15.14	42	Venous loops and reduplications are rare manifestations of diabetic eye disease. The following definitions may be used but it is advised to check: • A venous loop is defined as a localised looping deviation of the vein from its normal linear course. • A venous reduplication is defined as a localised venous segment with two or more reuniting	**Thank you for your comment.. , Recommendations on eye disease were reviewed by the Director of the National Diabetic Eye Screening Programme and changes were incorporated into the recommendations.**

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				parallel branches. Also, whilst the precise identification of vascular malformations is within the expertise of an ophthalmologist, most physicians only see "dots and blots" on fundoscopy. Suggest referral on the basis of "dots and blots" and let the experts decide what the malformations are.	
Juvenile Diabetes Research Foundation	NICE FULL	1.3 7.2.6	18 19 131	Again, JDRF welcomes the guidance setting out the importance of structured education for people with type 1. However, they need a wider range of educational approaches and support 'at the right time, in the right place and in the right way' (All Party Parliamentary Group for Diabetes, 'Taking Control' (2015), p.21). Although structured education is considered to be the gold standard of diabetes care, drastically low provision and uptake currently means that far too few people are receiving any support at all and over-prescriptiveness about what counts as structured education can be a major barrier to people receiving any kind of support. The APPG report found that a suite of interventions is needed - alongside structured education – to provide	Thank you for your comment. We have some sympathy for these suggestions but looking for evidence for these was not prioritised during the scoping process and therefore the GDG cannot make a recommendation. This matter has been flagged to the NICE guideline surveillance team.

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				other forms of learning opportunities and support through, for example, peer support groups, taster sessions, family and carer-focused training, emotional and psychological support, and better signposting to existing online support and services.	
North West Commissioning Support Unit	NICE	1.3	18 21 25	Update recommends offering all type 1 diabetics a structured education programme e.g. DAFNE, and offer this programme 6-12 months after diagnosis. The stipulation of a time period appears to limit the offering of education programmes after 12 months and those patients may be disadvantaged. Should the offering not be considered after periodic assessment by the specialist team?	Thank you. We have amended this recommendation text: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] **1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes.**

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					[new 2015].
Foot in Diabetes UK	Nice	1.13.2	36	At the bottom of the list add Peripheral arterial disease PAD	Thank you for your comment. This has not been added since PAD is not a risk factor – it **is** a type of arterial disease
Diabetes UK	NICE	1.15.21	43	We appreciate that the guidance notes the risk of orthostatic hypotension, but we feel a low cut-off for BP should also be stated. We advise that the Joint British Societies guidance should be followed: "Blood pressure should be maintained at 130/80 mm Hg and consideration of lower values (120/75–80 mm Hg) as a target in younger type 1 diabetes (aged <40 years) with persistent micro albuminuria". (JBS3 Heart 2014; 100:ii1-ii67).	Thank you for your comment. This topic was not prioritised for update. This matter has been flagged to the NICE guideline surveillance team.
Association of British Clinical Diabetologists	NICE	1.3.1	18	What is implied by the expression 'for example' (for example DAFNE). Is any preference being expressed for this particular programme by using this expression ? The full version shies away from making a definitive recommendation on whether DAFNE should be recommended as the sole education programme.	Thank you for your comment. In the absence of head-to-head comparisons the guideline development group did not feel able to recommend one unequivocally over all others, although they felt comfortable steering users towards DAFNE.
INPUT	NICE	1.3.1	18	This needs to include people who have been diagnosed	Thank you for your comment. We

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Patient Advocacy				for more than 12 months and have not yet been offered structured education, especially if their HbA1c is above target.	have amended this recommendation. Text: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] 1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes. [new 2015]
Juvenile Diabetes Research Foundation	NICE	1.3.1 7.2.6	18	We agree that structured education should be offered to people at a time that is clinically appropriate for a person within the first 12 months of diagnosis. However, for structured education to have real benefit,	Thank you for your comment. 'Refresher courses' were not in our scope. We did not look for the evidence and therefore the GDG are

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	FULL	12	131	people with type 1 also need to receive 'refresher courses' throughout their lives to enable them to renew key skills, update them on the latest theory and treatments, and support them to feel that type 1 diabetes is manageable to overcome potential 'diabetes burnout' or loss of motivation to self-manage the condition effectively.	unable to make recommendations in this area. This matter has been flagged to the NICE guideline surveillance team.
Juvenile Diabetes Research Foundation	NICE FULL	1.3.1 7.2.6 12	18 131	It is also vital that people living with type 1 diabetes for more than a year are encouraged to attend diabetes education if they have not already done so. We hear of far too many cases of people living with type 1 finding out about, and seeking access to, diabetes education only to be told they do not qualify for a place as they have been diagnosed with the condition for longer than one year. It is vital that everyone is offered the opportunity to develop the essential skills they need to self-manage type 1 as effectively as possible. This will reduce the likelihood of costly complications in the future.	Thank you for your comment. We have amended this recommendation text: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] 1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is

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					clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes. [new 2015]
Diabetes UK	NICE	1.3.1	18	We feel this recommendation is too prescriptive. Some people with Type 1 diabetes will benefit from a course such as DAFNE earlier than 6 months and some later than 1 year. Education should be offered at the point appropriate to the individual. People with diabetes want flexible approaches to learning that fit with their lives and this should be made clearer in the guideline. We would recommend that individuals should be offered appropriate learning and education at the point of diagnosis, some structured education within 12 months and DAFNE or equivalent within 24 months. We are also concerned that the guidance does not adequately cover people with existing Type 1 who have not been offered structured education previously. Education should be available whenever people need it, and not only in the two years following diagnosis.	Thank you for your comment. We have amended this recommendation text: 1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis. [new 2015] 1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes. [new 2015]
Diabetes	NICE	1.11.3	34	While capillary ketone measurement can be helpful	

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UK				there is a concern that if using ketones rather than serum bicarbonate levels to assess recovery from DKA, fluids may be terminated earlier that desirable, especially in people who are dehydrated.	Thank you for your comment. The management of DKA was not in the scope, which in this context only asked about the use of blood ketone monitoring. This matter has been flagged to the NICE guideline surveillance team.
Association of British Clinical Diabetologists	NICE	1.1.4	14	"Consider further specialist investigation ..." Does this statement imply that the test is specialised or that the test should only be carried out in specialist centres ? It may be better to remove the word specialist or clarify further.	**Thank you for your comment.. We have removed 'specialist'.**
Juvenile Diabetes Research Foundation	NICE FULL	1.3.2 7.2.6 14	18 131	JDRF supports providing people with alternative forms of support and training but this should be offered to all people with type 1 alongside structured education opportunities rather than simply those unable to participate in group structured education. This will ensure that education is tailored to the needs of the individual and their family or carer at the right time to meet their personal and family circumstances.	Thank you for your comment. Recommendation 1.3.2 is about structured education, not about alternative forms of support which was not in the scope. This matter has been flagged to the NICE guideline surveillance team.
Diabetes UK	NICE	1.13.4	37	We would like clarity over lipid targets for people with Type 1 diabetes as the lipid modification guidelines do	**Thank you for your comment. We did not review this topic because**

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				not state a target. The recommendation to "aim for a greater that 40% reduction in non-HDL cholesterol" is not helpful for people with Type 1 diabetes and does not give a lower cut off.	**it was covered by the Lipid Modification GDG. However we think the evidence for use of statins comes from trials of statin treatment and not from treating to a target and so does not allow specification of a lower cut-off.**
Royal College of Nursing	NICE	1.14.4	39	Inclusion of the word '*consider*': national Diabetic Ketoacidosis (DKA) guidance recommends continuation of basal insulin - it would therefore be clearer if the word 'consider' is not included.	**Thank you for your comment. We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the**

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					patient.
Association of British Clinical Diabetologists	NICE	1.1.5	14	In outlining antibody testing strategies, it would be helpful to add clarification to the effect that "..carrying out tests for diabetes specific auto-antibodies, **with one or more being positive**, reduces the false negative rate."	Thank you for your comment.. We have accepted the suggested wording.
Successful Diabetes	NICE	1.2.4	17	Line 19. Add 'and sources of self-help support, including for emotional and psychological needs'	Thank you for your comment. This recommendation is from the 2004 recommendation, and was not prioritised for update. This matter has been referred to the NICE guideline surveillance team.
Dexcom	NICE	1.2.4	17 18	Care process and support section discusses that avoidance of hypoglycaemia should be part of the plan. There should be a mention of the utility of CGM as a way to avoid hypoglycaemia: both as a short term diagnostic tool and as a personal use device for patients that have problematic hypoglycaemia. Data shows that CGM is the most effective tool for avoidance of hypoglycaemia – even when compared to multiple SMBG tests daily	Thank you for your comment.. This is a 2004 recommendation which was not in the scope for us to update. Therefore the Guideline Development Group did not have a remit to change this recommendation. 2004 recommendations that were not in the scope for the update can only be changed when it is absolutely necessary (that is, there is a patient

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					safety issue if the recommendation is not updated). This matter has been flagged to the NICE guideline surveillance team.
Juvenile Diabetes Research Foundation	NICE FULL	1.3.3 7.2.6 15	19 131	JDRF supports the importance of including family and carers in education to 'develop attitudes, beliefs, knowledge and skills to manage diabetes' as part of the vital support needed by people affected by type 1 diabetes.	Thank you. We did not review the evidence as this was not in the scope. This matter has been flagged to the NICE guideline surveillance team.
Bayer Plc	NICE	1.6	24	**Self-monitoring of blood glucose** The previous (2004) type 1 diabetes clinical guideline included recommendation 1.8.2.4 (*Self-monitoring should be performed using meters and strips chosen by adults with diabetes to suit their needs, and usually with low blood requirements, fast analysis times and integral memories*), which has been removed from the 2014 draft guideline. The rationale for this is given as *"This recommendation has been deleted because it is no longer relevant. Technology for blood glucose meters has advanced since 2004. All blood glucose meters have integrated memories and fast analysis times."* However, whilst it may be the case that all	Thank you for your comment. The GDG have added the following recommendation: *Take patient preferences into account when choosing meters and ensure meters meet current ISO standards*

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				meters have integrated memories and fast analysis times, there are other differentiating attributes between the meters that may be very important for the accommodation of individual patient needs, especially in relation to user acceptability and ease of use e.g. • Accuracy and precision • Size of memory e.g. for people who need to maintain a record for the DVLA • Size and ease of use e.g. for people with poor dexterity and other needs such as arthritis • Portability • Ability to download and share the results using a computer • Display appearance and other features designed for people with visual impairment • Option to log carbohydrates or insulin units • Also for patients using continuous subcutaneous insulin infusion it is important to ensure that a compatible glucometer is used that sends blood glucose results directly to the insulin pump. People with type 1 diabetes should be provided with full and correct information on all of the available options	

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				and should be actively involved in the decision regarding meter choice. This will facilitate the selection of the meter that is best suited to an individual's circumstances, and allow them to use the meter effectively. In turn, this might be expected to lead to greater engagement in self-management, such as through higher SMBG frequency and better medication adherence and therefore improved glycemic control. We suggest that a recommendation should be included in line with that in the diabetes in children and young people guideline (1.2.61) which states *"Offer children and young people with type 1 diabetes and their family members or carers (as appropriate) a choice of equipment for monitoring capillary blood glucose in response to adjustment of insulin, diet and exercise."*	
Dexcom	NICE	1.10.5	31	CGM should be considered as one of the strategies for managing patients with impaired awareness of hypoglycaemia. Frequent hypoglycemia is associated with a downshift of glycemic threshold for endocrine and symptomatic counterregulatory responses toward low blood glucose, causing hypoglycemia unawareness and subsequently an increase of hypoglycemia problems.	Thank you for your comment. We did look for this evidence. Most of the trials excluded people with IAH until the Ly study. We enshrined our review in recommendation 1.10.7 bullet 3.

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				Early detection and scrupulous avoidance of low glucose values can restore hypoglycemia awareness and reduce the risk of SH by an upshift of glycemic thresholds. CGM provides the best tool to achieve this.	
Successful Diabetes	NICE	1.1.6	15	Line 16. Delete 'to determine pace of education' as assessment of emotional state is important in its own right and has no relationship with pace of education. Add 'and acknowledge the emotional burden of being diagnosed with Type 1 diabetes'. See also general comments below. Add new bullet 'discuss and agree pace of education'	Thank you for your comment. This is a 2004 recommendation which was not in the scope for us to update.therefore the Guideline Development Group did not have a remit to change this recommendation. 2004 recommendations that were not in the scope for the update can only be changed when it is absolutely necessary (that is, there is a patient safety issue if the recommendation is not updated). We have added some text to the 'living with diabetes' section of the full guideline (section 1.1): 'Emotional and psychological support, both at initial diagnosis and on a continuing basis, will enhance

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					the patient's ability to live with diabetes.' We have flagged this matter to the NICE guideline surveillance team.
Northumbria Healthcare NHS Trust	NICE	1.1.6	15	We feel the initial diabetes assessment should also take alcohol consumption into consideration and should be mentioned specifically here	This is a 2004 recommendation which was not in the scope for us to update. We have flagged this matter to the NICE guideline surveillance team.
Successful Diabetes	NICE	1.3.4	19	Line 19: add after 'integral part of diabetes care', 'so that they can successfully live with it'	Thank you for your comment, which we think is referring to recommendation 1.3.3 not 1.3.4. We don't think the extra words are required.
Diabetes UK	NICE	1.4.3	20	We are concerned that this point could be misconstrued to mean that people with Type 1 diabetes should not follow a low GI diet. A healthy diet usually contains some low GI foods and there are instances, particularly around exercise, where low GI foods can be beneficial. We recommend that this point is made clearer and include the need for a healthy balanced diet.	Thank you for your comment. Unfortunately, we found only negative evidence for the benefit of low GI foods on glycaemic control. As we were asked in the scope to make a recommendation about low GI diets we can only say they are not

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					indicated.
Dexcom	NICE	1.6.1	23	A1c measurements can have limited utility when measuring glycaemic fluctuations: A1c is also not an effective tool for measuring episodes or duration of hypoglycaemia. A1c is an average and therefore one should consider adding either a periodic CGM measurement or other metrics of glycaemic variability (SD or CV). It is the glycaemic variability that represents the greatest challenge to euglycemia	Thank you for your comment.This section is entitled HbA1c measurement and targets. Glucose monitoring is covered in a separate section.
Royal College of Physicians of Edinburgh	NICE	1.10.6	31	Avoiding setting lower glucose targets is not helpful in a patient with impaired awareness of hypoglycaemia and goes against current practice to try to avoid all hypos for at least 3 months, especially nocturnal hypos. Usually this can only be achieved by reducing insulin and relaxing control, especially at night. After 3 months, awareness may have improved and glycaemic control can be tightened up again.	**Thank you for your comment.This section is entitled HbA1c.Our review of the evidence shows that avoidance of hypoglycaemia is the key to restoring awareness. This means ensuring minimal exposure to glucose concentrations below the lower limit of the normal range not increasing exposure to glucoses above the higher limit. There are no data to support the setting of**

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					high targets for three month periods.
Diabetes UK	NICE	1.10.6	31	While we are aware of the findings of the Compass study that suggests that targeted education can reduce hypos irrespective of CSII and/or CGMS use, we feel this recommendation requires further thought. We are concerned that this recommendation is potentially dangerous to people with Type 1 diabetes. We recognise that this recommendation may be appropriate for highly specialised Type 1 centres, but are concerned that for most diabetes services there is a safety issue. In people who have reduced awareness of hypoglycaemia, a temporary relaxation in blood glucose targets can help ensure safety while measures such as intensive diabetes education are put in place.	Thank you for your comment. Our review of the evidence shows that avoidance of hypoglycaemia is the key to restoring awareness, and that it should not be necessary to permit hyperglycaemia for a period of time. We acknowledge that this requires careful monitoring, but the purpose of NICE guidance is to promote best practice, and we feel that this is what the current recommendation promotes.
Diabetes UK	NICE	1.6.12 1.6.13	25	We support the recommendation for frequent blood glucose monitoring as this will help overcome the difficulty that some people with Type 1 are facing in obtaining sufficient blood glucose testing strips.	Thank you for your comment.
Successful Diabetes	NICE	1.6.13	General	Line 21: add a further example after 'activities' 'or experimenting with new foods or activities, to gain feedback on their effects'	Thank you for your comment. Recommendations do not usually include qualifying information.

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Successful Diabetes	NICE	1.6.13	25	Line 10: add 'to the satisfaction of the adult with Type 1 diabetes' after 'achieved'	Thank you for your comment; however we consider this addition is unnecessary; the target will have been agreed between the adult with type 1 diabetes and the healthcare professional.
Dexcom	NICE	1.6.13	25	• Providing support of 10 SMBG tests/day for type 1 patients who meet specific criteria: CGM should be considered in this category as SMBG (even at 10x/day) still does not capture nocturnal hypoglycaemia and will not provide the same level of safety for people with hypoglycaemia unawareness as does CGM. While the cost per QALY may be deemed too high for UK thresholds, CGM is the only tool that can address both hypoglycaemia unawareness and nocturnal hypoglycaemia and should be considered	**Thank you for your comment. This recommendation is about testing with strips. CGM is dealt with separately.**
Faculty of Pharmaceutical Medicine	NICE	1.6.13	25	On the topic "Frequency of self monitoring of blood glucose", it is recommended to monitor blood glucose up to 10 times a day as per DVLA requirements. It may be appropriate to use "Continuous glucose monitor"	Thank you for your comment. CGM is considered elsewhere. CGM is not recognised as suitable for assessing the glucose concentration prior to

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				rather than conventional strip monitor in this case as continuous glucose monitor pose higher efficacy than conventional monitor safe guarding patient risk due to hypoglycemia.	driving
INPUT Patient Advocacy	NICE	1.6.13	25	• This implies that it is possible to attain an HbA1c of <6.5% on only 4 daily blood glucose tests, and may encourage CCGs to restrict numbers of blood glucose test strips prescribed. The guideline needs to make provision for people who need to test more frequently than 4 times per day in order to maintain an acceptable HbA1c.	Thank you for your comment. The first bullet point of this recommendation specifically addresses this concern.
Abbott Diabetes Care	NICE	1.6.13	25	We welcome the clarification on blood glucose testing and would recommend that hyperglycaemia is also considered. There is evidence to suggest that glucose variability is an important predictor of outcomes and hypoglycaemia and we suggest that the recommendation considers glucose variability and that increase glucose testing should be supported to assess glucose variability	Thank you for your comment. We think the current list of clinical indications is sufficient without the addition of "to assess glucose variability"

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Diabetes UK	NICE	1.6.15 1.6.16	26 26	We are concerned that the different targets for different times of the day are confusing for people with diabetes and may dis-incentivise them. We would suggest a clear target for blood glucose level at bedtime is stated. Depending on the time of the bedtime test relating to the evening meal, the draft recommendations suggest that a level as low as 5 would be acceptable before bed which we do not feel is appropriate as it may cause night time hypoglycaemia. We note that DAFNE recommend a target of 6.5-8mmols/l and suggest that target should be considered.	**Thank you for your comment. The targets are different because the evidence base for each is different.**
Diabetes UK	NICE	1.6.16	26	The guideline should clearly state how long after a meal people with Type 1 diabetes should expect to achieve these blood glucose levels, eg 1 or 2 hours.	Thank you for your comment. We have amended the recommendation to specify timeframe for postprandial testing: 1.6.14 Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5–9 mmol/litre at least 90 minutes after eating. (This timing may be different in pregnancy – for guidance on plasma glucose targets in pregnancy, see the NICE

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					guideline on diabetes in pregnancy.) [new 2015]. The rationale for the target is explained in the full guideline, please see pages 229 -233.
INPUT Patient Advocacy	NICE	1.6.17	26	Patients should be advised to use a blood glucose meter which complies with ISO 15197:2013 (all blood glucose meters available in the UK will comply from the end of May 2016). Blood glucose test strips cannot be prescribed in the same way as a generic drug and accuracy must not be compromised in an attempt to save money.	Thank you for your comment.NICE guidance assumes that devices are of appropriate standard, properly maintained, and used by those trained to use them. We have added a recommendation: 1.6.11 Take the person's preferences into account when choosing blood glucose meters, and ensure that meters meet current ISO standards. [new 2015]
Abbott Diabetes Care	NICE	1.6.17 1.6.18	26	We support the recommendations on empowering people to self-monitor blood glucose. We would suggest that, people with type 1 diabetes are routinely taught how to use the	**Thank you for your comment. We have not specifically looked at these facilities, but note that the recommendation is compatible with their use.**

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				download data facilities available and accessible today and use the ensuing reports to support the interpretation of results by both HCP and patient.	
INPUT Patient Advocacy	NICE	1.6.18	26	This support should include consideration of patient choice of glucose monitor that fits in with their lifestyle and clinical needs. This measure will help prevent CCGs from attempting to save money by changing all their patients with diabetes to a single, low cost blood glucose monitoring system. One system is not suitable for everyone, and patients must have a choice if they are expected to make frequent daily use of this equipment.	Thank you for your comment.. We have added a recommendation about choice of monitors. 1.6.11 Take the person's preferences into account when choosing blood glucose meters, and ensure that meters meet current ISO standards. [new 2015]
Successful Diabetes	NICE	1.3.5	General	Line 22: add 'both proactively, and in response to questions and concerns' after 'onwards'	Thank you for your comment.Thank you. We do not feel the changes are necessary.
Juvenile Diabetes Research Foundation	NICE FULL	1.3.5 7.2.6 16	19 131	We strongly support efforts to make people affected by type 1 diabetes more aware of the value of education courses at all points of contact. We also support every opportunity for healthcare professionals to refresh key skills messaging in routine appointments throughout a person's 'diabetes journey'.	**Thank you for your comment.**

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Royal College of Pathologists	NICE	1.6.2	23	If HbA1c is measured more often as suggested, clinicians must take into account the fact that HbA1c concentration reflects time-weighted average blood glucose concentration over the previous three months so changes in average blood glucose within the past three months will not fully be reflected in the HbA1c result.	Thank you for your comment.. We believe readers will take this into account.
Royal College of Pathologists	NICE	1.6.2	23	More appropriate here to state 'Use HbA1c methods that are calibrated according to ….. (it is the method that is calibrated, not the results)	Thank you for your comment. The recommendation is 1.6.3. We have amended it to: "*Use methods to measure HbA1c that have been calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation. [new 2015]"*
Medtronic	NICE	1.6.20	26	As per comment 1 on the Full guideline, we feel it would be pertinent to remove this recommendation in order to avoid any undue confusion when the DAP recommendations are published.	Thank you for your comment. On general principle, if a NICE recommendation disagrees with previously published guidance, this will be clearly sign-posted in the newer guidance.
Novo	NICE	1.10.7	31	Insulin degludec may be considered as part of new	Thank you for your comment.We did

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Nordisk Ltd				insulin regimens and strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, prior to insulin pump therapy.	not find any evidence on the use of degludec in people with hypo unawareness
Dexcom	NICE	1.6.21	26	Consider adding the criteria listed in 1.6.13 (discussed above) to this section. Specifically that CGM protects against nocturnal hypoglycaemia and should be listed as one of the criteria for when CGM is used.	**Thank you for your comment.The situations are not identical. For example, we would not consider CGM for all car drivers**
Medtronic	NICE	1.6.21	26	As per comment 3 on the Full guideline, we suggest that two further patient groups are considered within this recommendation: patients with frequent hyperglycaemic events, and patients with poor control of HbA1c. Further, "complete loss of awareness of hypoglycaemia" should be reworded to "impaired awareness of hypoglycaemia", to ensure consistency with clinical literature and terminology, and parity with trial inclusion criteria.	Thank you for your comment. We did look at data for CGM for hyperglycaemia and that given the recommendation of supporting increased frequency of SMBG, the evidence does not suggest CGM is a cost effective alternative to SMBG up to ten tests per day. We conducted a sensitivity analysis where we assumed CGM was able to reduce HbA1c to 6%. This did not change the results. We would need evidence to

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					recommend CGM for people with "frequent hyperglycaemic events – presumably DKA – for which there is none and the issue of high HbA1c we did consider but should review. The GDG did not wantt to recommend major use of CGM and therefore restricted this particular recommendation to complete loss of awareness comparable to the DVLA criterion for lack of fitness to drive. CGM has never been shown to improve awareness but it does provide electronic awareness when there is no patient awareness.
Juvenile Diabetes Research Foundation	NICE FULL	1.6.21 8.4.8	26 252	**JDRF firmly supports the Institute's recommendation advising providers to consider the use of CGM to address hypoglycaemia in adults with type 1 diabetes.** Hypoglycaemia is a significant risk posed by intensive insulin therapy and is also known to be a primary barrier to glycaemic control.	Thank you for your comment. **We have appropriately incorporated the Pickup 2011 data into our meta-analysis and it does not change the results or our recommendation.**

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				However, we request revision of draft recommendation 57 to reflect better the evidence supporting the efficacy of CGM in reducing HbA1c in adults with type 1 diabetes especially for those who have high baseline HbA1c levels. This recommendation is based on the subgroup results reported on by Pickup et al. in their IPD meta-analysis, results from individual randomised controlled clinical trials included in NICE's evidence review, and Endocrine Society/European Society of Endocrinology co-sponsored Clinical Practice Guidelines for Continuous Glucose Monitoring (http://www.ese-hormones.org/guidelines/docs/ESEJointEndocrineSocietyGuidelines.pdf and http://press.endocrine.org/doi/pdf/10.1210/jc.2010-2756). We specifically note that the IPD meta-analysis from Pickup et al., which aggregated and analysed individual patient data from randomised controlled trials examining the impact of real time continuous glucose monitoring compared with self-monitoring of blood	

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				glucose established that CGM reduces HbA1c and that reductions are greatest in those with higher baseline HbA1c and those who use CGM consistently. The IPD from Pickup et al. also indicates that CGM use reduces exposure to hypoglycaemia. (Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self-monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011;343:d3805.) Below we highlight our recommendations for revising recommendation 57. 57. ~~Consider~~ Offer real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have a baseline HbA1c equal to or greater than 7% or who have any of the following that persist despite optimised use of insulin therapy and conventional blood glucose monitoring: - more than 1 episode a year of severe	

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				hypoglycaemia with no obviously preventable precipitating cause - complete loss of awareness of hypoglycaemia frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities extreme fear of hypoglycaemia. [new 2015]	
Abbott Diabetes Care	NICE	1.6.21	26	We would suggest that CGM be considered to assess and reduce glycaemic variability	Thank you for your comment The recommendation has been changed to allow CGM to be used to address specific problems with hyperglycaemia, as well as hypoglycaemia"
Diabetes UK	NICE	1.6.21	26	Regarding CGMS, we would ask for some clarity over the phrasing "…any of the following that persist…" We feel that it should be made clearer that CGMS should be considered if a person with diabetes has one or more of the following list.	Thank you for your comment. We are sorry, we don't fully understand the question but have tried to answer it.We would use CGM if the problems persist (i.e. continue) after optimised use of insulin therapy and conventional monitoring – seems perfectly clear to us that we don't recommend CGM to people not

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					using best practice for self-management i.e. flexible insulin therapy as taught in structured education. We did not discuss the use of CGM in people whose services can't provide them with structured education – maybe it will just work but we doubt it and there certainly isn't any evidence.
Diabetes UK	NICE	1.6.21	26	We would like to see "frequent hypos with or without awareness" added to the list.	**Thank you for your comment.. There is no evidence to show improved awareness of hypoglycaemia with CGM, and the use of CGM in those without awareness is because it provides an artificial awareness. There is no evidence of benefit on non-severe hypoglycaemia**.
Successful Diabetes	NICE	1.7.12	29	Line 11: add 'emotional' before 'psychological and psychosocial'	**Thank you for your comment. The GDG consider that 'emotional' is included in 'psychological', and we feel that the term**

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					'psychological' is preferable to 'mental health / psychiatric' which is the newer NICE terminology so this has not been changed.
INPUT Patient Advocacy	NICE	1.6.23	27	Patients who meet these criteria but are attending a clinic which is not a centre with expertise in the use of continuous glucose monitoring are at risk of missing out on this strategy unless clinics are encouraged to refer patients for further assessment.	**Thank you for your comment. We agree, but the alternative is inappropriate use and inadequate training in CGM**
Diabetes UK	NICE	1.6.23	27	We would ask for some clarity on what constitutes a centre of expertise in the use of CGMS. We feel that it is important for this standard to be clearly set out by NICE to ensure that people with diabetes are not subject to poor quality care and all people with Type 1 diabetes should have access to a centre of excellence.	Thank you for your comment. NICE is not empowered to designate centres of expertise. The word is intended to convey that centres should have personnel with experience is use of CGM and the facilities to support patients adequately in terms of training and back-up.
	Nice	1.13.7	37	Adding Peripheral Arterial disease – to read Provide intensive management for adults who have had myocardial infarction, stroke or a diagnosis of peripheral arterial disease according to relevant non-diabetes guidelines.	Thank you for your comment. We have updated the guideline as suggested.

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Diabetes UK	NICE	1.7.14	29	We would like to make the point that the BMI cut off might need to be ethnic specific.	Thank you for your comment. We apologise for the oversight. The document has been amended to reflect current opinion that a lower BMI is considered to confer increased metabolic risk in people of Asian ethnicity than in populations of White ethnicity. Recommendation 1.7.14 now reads as follows: "Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m2 (23 kg/m2 for people from South Asian and related ethnic minority groups) or above wants to improve their blood glucose control while minimising their effective insulin dose. [new 2015]."
Faculty of	NICE	1.13.8	37	It is advised to define 'albuminuria' i.e. how much	**Thank you for your comment.**

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Pharmaceutical Medicine		1.15.18	43	albumin? And how is this measured?	**Albuminuria is defined in the NICE CKD guideline.**
Successful Diabetes	NICE	1.14.8	40	Line 2/3: remove brackets	**Thank you for your comment. We have made the change.**
Diabetes UK	NICE	1.15.8	41	The need for retinal screening post islet cell or pancreas transplant, even if insulin is no longer required, should be included as retinopathy can still appear or progress.	**Thank you for your comment.We agree, but this will happen if the current recommendations are followed as stated**
Northumbria Healthcare NHS Trust	NICE	1.3.7	20	Recommendation might be amended to take account of our comment 7 above so that DAFNE could be recommended for people with issues related to hypoglycaemia: "Consider the Blood Glucose Awareness Training (BGAT) programme or DAFNE structured education for adults with type 1 diabetes who are having recurrent episodes of hypoglycaemia"	Thank you for your comment. We did not find evidence to support this.
Successful Diabetes	NICE	1.6.4	23	Line 25: add 'ideally, in advance of the next consultation' after 'measurement'	Thank you for your comment. There is a view that having the HbA1c result yourself before a consultation is helpful but we are not aware of data to show benefit.
Medtronic	NICE	1.8.2	29	As per comment 6 on the Full guideline	Thank you for your comment.. We believe readers will take this into

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					account.
Diabetes UK	NICE	1.9.1	30	We would like to see a recommendation around simultaneous pancreas and kidney transplantation for those people with Type 1 diabetes who need kidney transplantation.	**Thank you for your comment.In practice this is what will happen under 1.9.2, but our remit did not include a review of renal transplantation and it is therefore difficult for us to specify this in a recommendation.**
Faculty of Pharmaceutical Medicine	NICE	1.10.9	32	What is a fast-acting form of glucose? Suggest including examples of fast-acting form of glucose	Thank you for your comment. This is a 2004 recommendation which the GDG did not have a remit to update.
Faculty of Pharmaceutical Medicine	NICE	1.6.5	24	Suggest using a more accurate description of altered red cell turnover than that currently used = "disturbed".	Thank you for your comment.This is a 2004 recommendation which the GDG did not have a remit to update.This matter has been flagged to the NICE guideline surveillance team.
Royal College of Physicians of Edinburgh	NICE	1.7.4	27	The indication to recommend only Detemir as the basal insulin is promoting a single pharmaceutical company and the evidence that it provides better glycaemic control and less hypoglycaemia compared to NPH (isophane) insulin is uncertain. References should	Thank you for your comment. The guideline recommends a specific treatment rather than promoting a whole company. We have also recommended considering other

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				therefore be reviewed.	types of insulin if detemir twice daily is not appropriate. References were carefully reviewed in our systematic review process.
Diabetes UK	NICE	1.7.4	27	We recommend that the need to personalize treatment is given greater priority. While we support the recommendation for basal bolus regimens, there are certain people with diabetes who may need less intensive regimens at certain times. The recommendation of detemir twice daily as a first choice for basal insulin therapy is too prescriptive and does not allow for individual patient choice and clinical judgement. While we appreciate that the draft guidance goes on to consider other insulin regimens, this is not given sufficient priority and does not allow the clinician to personalize treatment to the needs of the individual.	Thank you for your comment. We understand your point, but we have considered a wealth of evidence in order to arrive at recommendations about best treatment for people with type 1 diabetes, and if we start with a statement that implies "anything goes" we detract from that message.
Novo Nordisk Ltd	NICE	1.7.4	27	Novo Nordisk supports the committee's decision to place twice daily insulin detemir (Levemir®) as first line for basal insulin replacement. • The guideline suggests insulin glargine as an option if patients do not want twice daily injections.	Thank you for your comment. We have revised the recommendation which now gives the option of once daily detemir or glargine if twice-daily basal insulin injection is not acceptable to the person, or once-

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				However the insulin detemir license states 'The duration of action is up to 24 hours depending on dose providing an opportunity for once or twice daily administration.' Therefore we request the wording allows for consideration of once daily insulin detemir before changing the patient to another insulin. Evidence supporting this includes: Heller S et al, 2009. 31(10):2086-2097. Bartley P et al, Diabetic Medicine, 2008. 25:442-449. Vague P et al, Diabetes Care, 2003. 26(3):590-596. Zachariah et al, Diabetes Care, 2011. 34:1487-1491.	daily insulin glargine if insulin detemir is not tolerated. This was based on the revised economic analysis.
Sanofi	NICE	1.7.4	27	We believe the recommendation that twice daily insulin detemir be used as the first-line insulin in patients with type 1 diabetes is not supported by the clinical or economic evidence and furthermore will unnecessarily restrict patient and clinician choice. Patient choice is enshrined as a core principle of the NHS Mandate from the Department of Health for 2014-15 and the NHS constitution. The proposed recommendation preferring one regimen above all other regimens takes away the flexibility and choice which	Thank you for your comment. In the guideline we acknowledge that there is uncertainty in the ranking, which has been clearly noted in the discussion and conclusion sections of Appendix M. We also acknowledged that the quality of the RCT evidence used in the NMA is generally low, which has been clearly noted in the grading of

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				are so important for patients and clinicians. Such an action can only be justified if there is clear and irrefutable evidence to support it, and we believe this is not the case. The clinical evidence is heterogenous, leading to largely equivocal results from the network meta-analysis (NMA). As a result the evidence synthesis does not support a ranking of the insulins and insulin regimens, and does not clearly support a claim of superiority of insulin detemir b.d. over all the other insulins or insulin regimens. It is clear that most insulins have overlapping estimates of effectiveness, with all the analogue insulin regimens showing numerical improvement compared to all NPH regimens. The economic analysis which is relied upon to support this hierarchical recommendation is flawed as it does not capture the variation in dose which occurs clinically (in the real world) by different treatment regimen. Most importantly, the cost of insulin detemir when used as a b.d. regimen is significantly underestimated.	the evidence. Nevertheless, this represents all the current RCT evidence available in this area that the GDG had to use to inform its recommendation. However, the final GDG decision to recommend insulin detemir (twice daily) was based mainly on the conclusions of the economic model, which takes into account quality of life and costs as well as clinical effectiveness, and not on the treatment ranking or the NMA results only. We have added some additional analyses to explore the different doses issue. In a one way sensitivity analysis, only the daily dose of detemir twice daily was changed while all the other insulin regimens were kept constant; this showed that

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				In the model, all insulins are assumed to require 24 units per day to achieve their respective level of glycaemic control, whereas in the real world, dose requirements vary between insulins and by frequency of dosing. Indeed the clinical trials supporting the estimates of treatment effects that are relied upon in the model, show there was considerable variation in the dosage requirements of the different insulins and insulin regimens. Correcting for these differences leads to a different conclusion on the regimen achieving the higher net monetary benefit (NMB); insulin glargine produces a higher NMB than insulin detemir b.d. The justification for favouring twice daily over once daily insulin administration is based on a single clinical study of insulin detemir, in which the authors concluded that "although some individuals may benefit from twice-daily dosing, the most suitable routine starting schedule for detemir in a basal-bolus regimen for type 1 diabetes is once-daily injection." The conclusion of the study contradicts the GDG's recommendation, and	up to an increase by 25% of the standard daily dose (24 units), detemir twice daily was still the most cost effective option. In another analysis, we estimated the average daily doses for each insulin regimen from the RCTs included in the network meta-analysis; also in this analysis detemir twice daily was the most cost effective option. For this reason the GDG did not believe the recommendation had to be changed. **We would also like to note that as part of the NICE consultation process, economic models are made available to stakeholders to test their reliability only. As stated in the NICE proforma that was**

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				furthermore the results cannot be assumed to be indicative of once daily vs. twice daily administration of other insulins. We suggest that the GDG revisits its evidence review in this regard and reconsiders its hierarchical recommendation accordingly.	**sent out along with the model, results calculated purely for the purpose of using alternative inputs cannot be accepted.**
Diabetes UK	NICE	1.8.3	30	We are concerned that the recommendations on needle length are not sufficient to allow a choice of needle length that will ensure that insulin is delivered into the deep sub-cutaneous tissue. People with diabetes may inject at an inappropriate depth without experiencing pain, local skin reactions and injection site leakages. This can significantly impact on diabetes management.	**Thank you for your comment.. We have not specified any needle length in the recommendations because the evidence did not support this. By not specifying a length, the choice of needle length is left open.**
Royal College of Physicians of Edinburgh	NICE	1.6.6	24	The target for HbA1c long term control has changed to less than 48 mmol/mol (6.5%). However, there is evidence (Currie et al) that mortality rates in T1DM are lowest when HbA1c levels average between 48 and 58 mmol/mol (6.5 and 7.5%). When this is lowered to below 48 mmol/mol (6.5%), there is an increased risk of hypoglycaemia and mortality rates start to increase. Therefore NICE should carefully consider whether the consequence of lowering this target will reduce	Thank you for your comment. We think you are referring to the Eurodiab study. There is no evidence that mortality is due to hypoglycaemia and lower HbA1c.

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				microvascular disease but, in doing so, increase mortality rates.	
Diabetes UK	NICE	1.6.6 1.6.7 1.6.8	24	We would like to see much greater prominence to the recommendation of agreeing an individualized target HbA1c especially in relation to the potential of problematic hypoglycaemia. We are concerned about the safety of lowering the target HbA1c level to the level recommended as this risks increasing episodes of hypoglycaemia for people with Type 1 diabetes. This lower target could also be seen as unachievable and so dis-incentivise them to achieve it. We also question how many people could achieve the lower target. For these reasons we believe that a target range for HbA1c is stated, and it should be made very clear that any target should be set in consultation with the person with Type 1 diabetes taking into account factors such as daily activities, aspirations, complications, co-morbidities, occupation and history of hypoglycaemia.	Thank you for your comment. We think you are referring to the Eurodiab study. There is no evidence that mortality is due to hypoglycaemia and lower HbA1c.
Novo Nordisk Ltd	NICE	1.7.5	28	Novo Nordisk notes the omission of insulin degludec (Tresiba®) and request that it is included as an option for selected patients with Type 1 diabetes.	Thank you for your comment. Our network meta analysis (NMA) did not show any beneficial effect for

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				• Insulin degludec is a basal insulin with a long duration of action and stable action profile that results in a glucose lowering effect beyond 42 hours and a lower day-to-day variability in glucose-lowering effect compared with insulin glargine (Tresiba® SPC) Insulin degludec has an important place in therapy for patients at high risk of hypoglycaemia, those needing a longer acting insulin once daily with low variability or those needing flexibility in dosing. These attributes mean that insulin degludec could be considered in patients who struggle with stable glucose control with insulin such as frequent sufferers of diabetic ketoacidosis and those being considered for insulin pump therapy.	degludec in terms of major/severe hypoglycaemia compared to other strategies. We did not include nocturnal hypoglycaemia as a critical outcome in our NMA. Results from the economic analysis, which considered HbA1c reduction and severe hypoglycaemic events, show that degludec has been dominated in the base case as well as all sensitivity analyses by detemir twice daily. This was the case also in a sensitivity analysis where the average insulin doses from the RCTs included in the network meta-analysis were used. We do acknowledge the variation in individual response in real practice and therefore we have added a further recommendation: *"Use other basal regimens only if the regimens above do not deliver*

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					agreed targets; in choosing an alternative insulin therapy, take account of the preferences of the person with diabetes and acquisition cost."
INPUT Patient Advocacy	NICE	1.8.4	30	Mention of cost makes it possible that cost will be the first consideration, rather than clinical appropriateness. Prescribing needles is not the same as prescribing a generic drug.	**Thank you for your comment. We have amended the recommendation.**
Diabetes UK	NICE	1.8.4	30	While we accept the principle of minimising cost, we would ask for this recommendation to be removed as it does not allow a clinician to use their own clinical judgement and may encourage the use of poor quality equipment.	Thank you for your comment. This is a clinical guideline; it does not replace clinical judgement.
Dexcom	NICE	2.2	48 49	Considering the rapid pace of medical technology innovation, the cost effectiveness and utility of CGM should be re-evaluated frequently. Easier to use, more accurate and improved reliability of devices will presumably enable better patient outcomes. Thus, CGM should be evaluated more frequently as it evolves and cost of device declines due to reduction/elimination of SMBG requirements when using CGM.	**Thank you for your comment. We are aware that a change in the cost of technologies may change their cost effectiveness. However, we have to make recommendations based on the costs applicable at the time of the guideline publication. Any change**

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					in costs will be taken into account when the guideline is next updated. This matter has been flagged to the NICE guideline surveillance team.
Medtronic	NICE	2.2	48	We would like to request re-wording of 'CGM systems' on line 28, as we feel that use of the word 'system' could be confused with CGM as part of a sensor augmented pump system, the cost-effectiveness of which was not assessed. A more appropriate wording in this section may be • '*stand-alone CGM'.*	Thank you for your comment."Stand alone" may mean people exclude the systems that read out through the pump. Therefore this wording has not been changed.
Medtronic	NICE	1.7.6	28	As per comment 5 on the Full guideline	**Thank you for your topic. This topic is not in the scope.This matter has been flagged to the NICE guideline surveillance team.**
INPUT Patient Advocacy	NICE	1.7.6	28	Clinicians should be encouraged to refer patients for further assessment at centres with greater insulin pump experience if they think the patient is unsuitable for insulin pump therapy but their HbA1c remains above target and the patient has expressed interest in insulin	**Thank you for your comment.Pumps are not in our remit. This recommendation is included as a cross reference to TA 151 and we are obliged to re-**

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				pump therapy.	**produce it verbatim.This matter has been referred to the NICE guideline surveillance team.**
Juvenile Diabetes Research Foundation	NICE FULL	1.7.6 9.2.1.11 64	28 291	We note that section 1.6.6 (p.24) of the draft guidance advises supporting adults 'to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term complications'. As a result we suggest that NICE should recommend considering revising the criteria of NICE Technology Appraisal 151, cited at 1.7.6, to enable adults to qualify for continuous subcutaneous insulin infusion (CSII) when HbA1c levels remain over 7.5 per cent rather than the current 8.5 per cent, despite efforts to address this. It is estimated that 15-20 per cent of adults with type 1 currently meet NICE criteria for insulin pump therapy. However, according to the Insulin Pump Audit, just 6 per cent of adults currently have access to this vital technology. Revising the criteria of Technology Appraisal 151 in this way may increase access to insulin pump therapy for adults and assist them to meet the recommended HbA1c target.	Thank you for your comment. This is not a decision for this guideline development group. We have passed your comment to NICE.
INPUT Patient	NICE	1.8.5	30	Injection technique needs to be taught and checked/refreshed annually, and include angle of	Thank you for your comment. Injection technique was not in the

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Advocacy				insertion, needle withdrawal time and needle length as well as site rotation.	scope for the update. This matter has been flagged to the NICE guideline surveillance team.
Diabetes UK	NICE	1.8.5	30	The guideline should include more detail on the absorption rates of human/analogue insulin. The Forum for Injection Technique recommend that the thigh and buttocks are the preferred site for injecting NPH, and the abdomen for injecting soluble human insulin. However rapid and long acting insulin analogues may be given at any of the injection sites as absorption rates do not seem to be site specific (FIT http://www.trend-uk.org/documents/FIT%20Recommendations%20Page%20view.pdf	Thank you for your comment. We had a review question on needle site and rotation, however no relevant evidence was found that matched our protocol inclusion criteria. As we are recommending analogue insulin in preference to older insulins, we do not see this as a major issue.
Successful Diabetes	NICE	2.3	49	Line 14: 'some people do not achieve' or 'are not able to achieve' rather than 'fail to achieve' Line 15: 'delete 'cannot' and replace with 'are not able' before 'to maintain them' Line 16: 'add 'are not offered or' before 'do not access'	Thank you for your comment. The wording has been updated
Northumbria Healthcare NHS Trust	NICE	1.6.9	24	Diabetes services should document the proportion of adults with type 1 diabetes in a service who achieve an HbA1c level of 53 mmol/mol (7%) or lower, without any episodes of severe hypoglycaemia	**Thank you for your comment. We agree this is good in principle but much more difficult to achieve as there isn't a standardised way of recording hypoglycaemia.**

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Medtronic	NICE	3.2	55	The NICE Diagnostic Assessment Programme is currently assessing CGM as part of a sensor augmented pump system: Type 1 diabetes: Integrated sensor-augmented pump therapy systems for managing blood glucose levels (The MiniMed Paradigm Veo System and the Vibe and G4 PLATINUM CGM system). We suggest that this is included in the 'Under Development' section.	Thank you for your comment. We have included it.
Juvenile Diabetes Research Foundation	NICE FULL	4.2	11 55	Although NICE Technology Appraisal 60 has been in place since 2003, just 2.4 per cent of adults with type 1 diabetes were offered access to structured education in the last National Diabetes Audit. Consequently, JDRF welcomes the prioritisation of diabetes education and information as an essential component of self-care. However, as set out in further detail later, we support the findings of the All Party Parliamentary Group for Diabetes' report, 'Taking Control: Supporting people to self-manage their diabetes' (2015), that education should be tailored to an individual's needs throughout their lifetime. Furthermore, more flexible forms of training and support are needed to encourage more	**Thank you for for comment. We're sorry,we are unsure which recommendation this relates to..**

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				people with type 1 diabetes to attend self-management education and to provide a more holistic model of care.	
Royal College of Nursing	NICE	12 10 20	11 24	% results should not be included. Laboratories stopped reporting these results in 2011 and 1.6.3 page 23 refers to International Federation of Clinical Chemistry IFCC standardisation of HbA1c. The inclusion potentially encourages practitioners to continue to convert back to % and continue to discuss results in % instead of mmol/mol the recommended IFCC standardisation of HbA1c results.	Thank you for your comment. We have included % results in brackets after IFCC standardised levels because some non-specialists will still find this easier; we do not think this encourages % use. We have also used % figures when reporting the literature if this is what was how the figures are presented in the studies.