Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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804	A Menarini Diagnostics	Full	8.3.1	139	Within the review of self monitoring of blood glucose we believe there is an opportunity to highlight opportunities arising from the application of new technologies. For example, healthcare professionals can now receive their patients full blood glucose history direct from their meters memory using smartphone app technology and Near Field Connectivity (NFC). This means that a person with diabetes can be closely and effectively monitored at vital times from anywhere in the world, and brings real cost saving efficiencies to patient management cand clinic workload.	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. Within the evidence review, a small, low quality trial showed no significant differences in blood glucose measures (HbA1c, fasting and postprandial blood glucose) at 3 months in SMBG using an automated glucometer (mobile phone) compared to a standard glucometer in people with unspecified current diabetes treatments (see section 8.3.2.2).
890	Abbott Diabetes Care	NICE	1.4.1 – 1.4.3	12 - 15	We would recommend that the medicine algorithm for blood glucose lowering therapy is consistent with current UK clinical practice, EASD and ADA guidelines recognising that patient care needs to be individualised based on a range of factors. We suggest that this algorithm is aligned with NICE appraisal guidance for specific treatments to ensure consistency and to ensure that innovation is embraced within the guidance.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
887	Abbott Diabetes Care	NICE	1.6.13	20	We would recommend that a cross reference is done with the type 1 guidelines for self-monitoring for people with type 2 diabetes who	Thank you for your feedback. The guideline development group did not review the evidence on the application of self-monitoring of blood

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					are on insulin who inject more than once per day. There is well documented evidence that people with type 2 diabetes on insulin are at the same risk of hypoglycaemia of which glycaemic variability is a predictor. Therefore, people with type 2 on insulin should have self-monitoring routine aligned with that of the draft NICE guidelines for type 1 diabetes. • Qu Y et al, Rate of hypoglycemia in insulin-treated patients with type 2 diabetes can be predicted from glycemic variability data. Journal of diabetes technology & Therapeutics, 2012 Nov; 14(11);1008-1012	glucose (such as frequency) specifically in people on insulin and therefore were not confident in making a specific recommendation in the absence of evidence.
888	Abbott Diabetes Care	NICE	1.6.14	21	We would propose that clinics and people with type 2 diabetes are encouraged to use the electronic data of their blood glucose systems and should therefore be supported to download their blood glucose meters to allow for easier interpretation of results to inform treatment decision making and that this should be included in the recommendation.	Thank you for your feedback. It was not within the scope of the guideline to consider blood glucose meters and how these systems should be used.
889	Abbott Diabetes Care	NICE	1.6.34	27	To support this recommendation and to assess if 'blood glucose rises markedly after meals', a self-monitoring regimen would need to be explicit to post meal and outlined within the glucose monitoring recommendation.	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. However, the Group recognised specific circumstances when self-monitoring

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						would be appropriate, including in individuals on insulin.
264	Action on Smoking and Health	Full	50	18	While we understand the reasons for removing *smoking cessation* from guidance as there is separate guidance for this subject, it is a concern that the dangers of smoking in particular for patients with diabetes is no longer mentioned in the Lifestyles section of the guidance either. Smoking is a risk factor for multiple complications of the disease, in particular heart disease, metabolic disorder, nephropathy and diabetic retinopathy. Compared to non-smokers with diabetes, people with diabetes who smoke have twice the risk of premature death and the risk of complications associated with tobacco use and diabetes in combination is nearly 14 times higher than the risk of either smoking or diabetes alone. [source: Haire-Joshu D & Thomas J. Gambling with addiction: Dangerous beliefs about smoking and diabetes. Diabetes Voice Smoking and diabetes special issue, 2005. 50: 15-18.] While most people are aware that smoking is a risk factor for respiratory and coronary diseases, the links with diabetes are less well known and should continue to be emphasised in the guidance.	Thank you for your feedback. It was not within the scope of the guideline to look at smoking in the diabetes population, although it is an important issue. There is a comprehensive set of NICE guidance on smoking cessation which will feed into the NICE pathway for the type 2 diabetes guideline. The NICE pathways online tool is the main interface through which clinicians now access NICE guidance and will enable easy navigation between type 2 diabetes and all pieces of related NICE guidance.
691	ASH Scotland	Full	50	18	Tobacco is a uniquely damaging product. While the number of people who smoke has halved in	Thank you for your feedback. It was not within the scope of the guideline to look at smoking in

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				/ general	the last 40 years, this still leaves 1 million people in Scotland with greatly increased risk of cancer, heart disease, stroke, dementia, arthritis and **diabetes**. Half of long-term smokers will die of a cause associated with their tobacco use, often after many years of debilitating illness, and tobacco is far and away the largest preventable cause of death. • Smoking has been established as a risk factor for Type 2 diabetes[1] and identified as a possible risk factor for insulin resistance, a precursor for diabetes.[2] • Compared to non-smokers with diabetes, people with diabetes who smoke have twice the risk of premature death. The risk of complications associated with tobacco use and diabetes in combination is nearly 14 times higher than the risk of either smoking or diabetes alone.[3] • Women who smoke during pregnancy are at increased risk of developing gestational diabetes and also increase the risk of their offspring developing diabetes later in life.[4] • Women who develop diabetes during pregnancy have a seven-fold increased risk of subsequently developing type 2 diabetes compared with women who have normal levels of glucose in pregnancy.[5] **Smoking is bad for diabetics**	the diabetes population, although it is an important issue. There is a comprehensive set of NICE guidance on smoking cessation which will feed into the NICE pathway for the type 2 diabetes guideline. The NICE pathways online tool is the main interface through which clinicians now access NICE guidance and will enable easy navigation between type 2 diabetes and all pieces of related NICE guidance.

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					• Smoking and diabetes both increase the risk of heart disease in very similar ways, and so when combined, they greatly increase the chances of suffering a heart attack or stroke. • Diabetic nerve pain is a syndrome that affects people with diabetes. Diabetic nerve pain usually occurs in peripheral regions or extremities, such as feet and legs, hands and arms. Smoking is known to increase the risk of nerve pain occurring.[6] • **Diabetic retinopathy is a common complication of diabetes, occurring when high blood sugar levels damage the cells at the back of the eye. If it isn't treated, it can cause blindness. Giving up smoking helps control diabetic retinopathy.**[7] • Reducing lifestyle-based risk factors such as smoking can improve the blood flow to vascular extremities. Both Type 1 and Type 2 diabetes are known risk factors in developing Peripheral Arterial disease, where a build-up of fatty deposits in the arteries restricts blood supply to leg muscles. These problems can lead to ulcers and infections that may lead to amputation.[8] However, smoking is the *most significant* risk factor.[9] Therefore, ASH Scotland encourages NICE to consider placing within the recommendations a fuller explanation of smoking as a cause of Type	

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					2 diabetes, and a more thorough set of evidenced recommendations around approaches to smoking and smoking cessation that can lessen harmful, risky behaviours which can lead to Type 2 diabetes developing. [1]Willi C, Bodenmann P et al: Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2007, 298:2654-2664. [2]ASH, Smoking and diabetes fact sheet, June 2012. Available at: http://ash.org.uk/files/documents/ASH_128.pdf [accessed 19 Feb 2015] [3]Haire-Joshu D & Thomas J. Gambling with addiction: Dangerous beliefs about smoking and diabetes. *Diabetes Voice:* Smoking and diabetes special issue, 2005. 50: 15-18. [4]Montgomery S. A very bad start: smoking, pregnancy and diabetes. *Diabetes Voice*: Smoking and diabetes special issue, 2005; 50: 30-32 [5]Bellamy L, Casas J-P, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *The Lancet*, 2009. 373: 1773-1779 [6]Diabetes.co.uk, *Diabetic Nerve Pain* [online]. Available at: http://www.diabetes.co.uk/diabetes-complications/diabetic-nerve-pain.html [accessed 19 Feb 2015] [7]NHS, Diabetic retinopathy [online], November 2013. Available at:	

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					http://www.nhs.uk/conditions/diabetic-retinopathy/Pages/Introduction.aspx [accessed 19 Feb 2015] [8]American Diabetes Association, Foot Complications [online], June 2013. Available at: http://www.diabetes.org/living-with-diabetes/complications/foot-complications/ [accessed 19 Feb 2015] [9]NHS, Peripheral arterial disease (PAD) [online], June 2014. Available at: http://www.nhs.uk/Conditions/peripheralarterialdisease/Pages/introduction.aspx [accessed 19 Feb 2015]	
174	Association of British Clinical Diabetologists	Full	121 -22	General	Individualised management – We strongly support the principle, but acknowledge there has until recently been limited data to inform this approach except in broadest terms. The GDG did not consider the attempt to quantify 'disutility' Vijan S et al *JAMA Intern Med.* 2014;174(8):1227-1234. doi:10.1001/jamainternmed.2014.2894. As one of the authors commented, "A typical person with type 2 diabetes who begins treatment at age 45 and reduces their A1c by 1% may gain up to 10 months of healthy life. At age 75, they may gain as little as 3 weeks of healthy life. Whether this is worth 10-15 years of pills and injections with potential side-effects is ultimately up	Thank you for your feedback and the reference of the simulated study that looked at the effect of treatment burden of intensive and moderate glycaemic control. The guideline development group has considered circumstances in which tight glycaemic control may not be beneficial in Recommendation 1.6.9 (NICE version) such as individuals who are unlikely to achieve longer-term risk-reduction benefits. It is envisaged that targets would be discussed and agreed with patients, taking into consideration individual circumstances including the benefits and risks of tight glycaemic control.
166	Association of British	Full	13	1.4	Algorithm in full version for first intensification of therapy and beyond makes no reference to	Thank you for your feedback. A reference box to NICE TAs for SGLT-2 inhibitors is included in the

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	Clinical Diabetologists				SGLT2I which have already been stated to have place in management at 1st and 2nd intensification points in NICE TAs.	algorithms for first and second intensification.
160	Association of British Clinical Diabetologists	NICE	18 -20	1.6	'Rise to 58 intensify to new target of 53 ' in isolation from other factors (ie hypoglycaemia risk in older people with CKD) appears a recommendation to put certain patients at risk. This statement should emphasise that the advice is directed to younger (aged <45) type 2 DM with the greatest lifetime risk of complications	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
163	Association of British Clinical Diabetologists	NICE	19	1.6.3	Fructosamine – should add 'if normal serum albumin and laboratory quality control in place'	Thank you for your feedback. The guideline development group does not agree that specific details are required for further clarity.
165	Association of British Clinical Diabetologists	NICE	20	1.6.10	May be prudent to mention need to re-evaluate accuracy of Hba1c in this situation as may be misleading if eg CKD and anaemia develops	Thank you for your feedback. Recommendation 1.6.3 notes "*HbA1c monitoring may be invalid because of disturbed erythrocyte turnover or abnormal haemoglobin type*". In addition, the following has been added to recommendation 1.6.10 "*Be aware that there are other possible reasons for a low HbA1c level, for example, deteriorating renal function or sudden weight loss*."
164	Association of British	NICE	20	1.6.9	Explicit guidance on relaxing control to 58 mmol/l in CKD will align with other national and	Thank you for your feedback. The guideline development group did not think that further

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	Clinical Diabetologists				international guidance	information on examples of comorbidities were necessary.
159	Association of British Clinical Diabetologists	NICE	21	1.6.15 -31	The clinical practice guidelines surely have to guide clinicians, particularly busy generalists in primary care. The separation of these proposed guidelines from the earlier completed NICE TAs on dapagliflozin , canagliflozin and most recently empagliflozin for combination therapy with other therapies for type 2 diabetes will create significant confusion as cross referencing to other documents in busy surgeries is not feasible. By appearing not to incorporate evidence about the newer agents in the main guideline (SGLT2 inhibitors and incretin mimetics) the useful shelf life of the guideline is likely to be limited. The cost of updating a guideline is a significant consideration. There is no specific mention in the main section about the use of modified release metformin in patients who are intolerant of standard release metformin, and for whom switching to an insulin secretagogue would be associated with risk. Clearly the cost is significantly higher, and the health economic analyses suggests little difference in tolerabilty, but this should be explicitly stated in the main document. The draft guidance makes much of the safety issues with sulphonylureas (hypoglycaemia) and metformin (in CKD4) , but does not make	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

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					similar reference to relative contraindications to pioglitazone (fracture risk , bladder cancer) or incretin modulators (risk of pancreatitis) .	
162	Association of British Clinical Diabetologists	NICE	21 -26	1.6.15-31	The use of pioglitazone in the treatment pathway for type 2 diabetes has largely fallen away due to the concern of most practising clinicians regarding the risk of weight gain, fluid accumulation, risk of heart failure and the impossibility of identifying people 'at risk of bladder cancer'. If the GDG wish to recommend this as an early treatment, there must be a fuler discussion of the risks associated with this treatment.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
167	Association of British Clinical Diabetologists	NICE	22	1.6.18	It would be helpful to have added sick day rules for metformin during (reversable) acute kidney injury where post recovery the need to reinstate metformin could be emphasised	Thank you for your feedback. It is outside the scope of the type 2 diabetes guideline to look at specific advice and information to be given to people with chronic kidney disease (CKD). The NICE clinical guideline on Chronic Kidney Disease was published in 2014 and includes updated recommendations on risk factors associated with CKD progression and also advice and education for people with CKD.
161	Association of British Clinical Diabetologists	NICE	22	1.6.19	The use of repaglinide as second line treatment, or first line if metformin intolerant will be controvesial. While recognising this glitinide was considered in detail regarding cost and phamacokinetic differences from sulphonylureas, ABCD-RCPL are unaware of any outcome studies demonstrating vascular	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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					benefit with repaglinide as is the case with gliclazide in the ADVANCE study. Conceptually the therapy could be stated to have a role in those with erratic eating patterns especially if only taking 1-2 meals daily. However given that polypharmacy involved in T2 DM care has been exhaustively documented to result in poor concordance with therapy, the option to use a tds therapy as opposed to a daily agent where there are no vital hypoglycaemia concerns is difficult to reconcile with best efforts to ensure adherence to therapy. In addition we are unaware of any evidence base for a direct clinical role of repaglinide as opposed to sulphonylureas in older patients and those with CKD.	The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
168	Association of British Clinical Diabetologists	NICE	22	1.6.19	The advice to start repaglinide but to then need to change to a sulphonylurea if HbA1c is 'not controlled' seems an unnecessary step as we are unaware of superior efficacy of sulphonylureas that would justify this approach . As stated previously we do feel the concordance issue with a daily as opposed to tds agent may well be the basis for greater efficacy which is a basis for suggesting that NICE consider parity of these 2 classes in the algorithm with an explicit statement that polypharmacy may lend itself to a single or twice daily as opposed to tds insulin secretagogue regime. In addition the advice as it stands suggests a switch from repaglinide to piogltazone if repaglinide does not control	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The health economic model had annual cycles and was not structured to consider short-term deterioration in control that could occur when

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					HbA1c, yet the time course of action of partially effective repaglinide with a precipitate switch to pioglitazone that takes several weeks to exert glycaemic benefit may lead to deterioration in glycaemic control which is not mentioned in this guidance	switching or intensifying treatment options.
170	Association of British Clinical Diabetologists	NICE	23	1.6.21	Gliptin with lowest acquisition cost takes no account of current and upcoming CVD outcome and safety data. There is a risk that advice to use lowest acqusition cost in selecting an agent from a class will lead to episodic mass switching in response to price changes. This is unpopular with patients and led to significant problems with insulin and with statins in the past.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
169	Association of British Clinical Diabetologists	NICE	23	1.6.23	SGLT2I class should be mentioned alongside gliptins as stated in NICE TAs on these agenst	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the

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						normal process for assessing the need to update TA guidance.
171	Association of British Clinical Diabetologists	NICE	24	1.6.26	Invitation to read another document to place SGLT2I is unrealistic if NICE objective is to support tailored individualised approach in the primary care setting	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
175	Association of British Clinical Diabetologists	Full	259 -60	8.4.18	It is clear that pharmacogenetics has the potential to allow more precise targeting of pharmacological therapies in type 2 diabetes, firstly by predicting those patients who are more or less likely to respond to particular agents, and secondly by predicting those at high risk of side-effects. NICE should include pharmacogenetics research in its recommendations.	Thank you for your feedback. The guideline development group recognises the importance in identifying patient characteristics that predict response or non-response to pharmacological blood glucose lowering therapies and therefore has made a research recommendation on this issue.
172	Association of British Clinical Diabetologists	NICE	29	1.7.2	Needs to be aligned with MHRA guidance on avoiding long terrm use of metoclopropamide	Thank you for your feedback. This section of the type 2 diabetes guideline was not prioritised for update following a stakeholder workshop and stakeholder consultation at the scoping stage. It was considered by the type 1 diabetes guideline and both guideline development committees agreed that the management of gastroparesis was likely to be similar between people with type 1 and type 2 diabetes. Therefore, 2 recommendations on the treatment of

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						gastroparesis from the type 1 diabetes guideline have been adopted in the type 2 diabetes guideline. In the recommendations, domperidone is recognised as having the strongest evidence for effectiveness but that it should only be used in exceptional circumstances when neither metoclopramide or erythromycin have been effective, based on the recent safety issues highlighted by the MHRA.
173	Association of British Clinical Diabetologists	NICE	34	2.3	Need for combination GLP1 analogues –SGLT2I weight and glycaemic efficacy studies	Thank you for your feedback. A research recommendation has been made to examine the effectiveness of non-metformin based treatment combinations.
158	Association of British Clinical Diabetologists	NICE Full version	General	General	There is a major difference in the recommendations made in these draft guidelines and the advice of the national specialist societies who have supported the recently revised ADA-EASD guidelines. While we respect the validity of the metanalyses which informed the discussions of the GDG, the commentary in the full guidance seems to suggest that there was a large degree of subjectivity in the ultimate conclusions. The fact that the group have published recommendations that are so far at odds with current clinical practice and recommendations from other published guidance, should prompt a pause for thought.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
349	Association of the	Full	13	1.4 figur	The medicine algorithm has been based on a relatively small number of randomized controlled	The health economic modelling considered both costs and quality of life impacts of long-term

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	British Pharmaceutical Industry			e 1	trials for individual therapies. This limited data drives the health economic modelling results and subsequent positioning of therapies. Assumptions are made regarding frequency, severity and timing of hypoglycaemia events; and durability of weight treatment therapy sequences and therapy intensification thresholds. When these are grouped together in the highly complex network meta-analyses, the health outcomes modelled across different treatment options may become homogenized. This evidence synthesis and health economic approach appears counter-intuitive, potentially leading to unclear results and guideline recommendations that appear primarily acquisition cost focused and fail to provide clear advice on the value for money of different approaches to achieving diabetic control in routine clinical practice.	complications (in part driven by changes in HbA1c), hypoglycaemia rates, treatment-related weight changes as well as drug acquisition and management costs (see 8.4.3 in the full guideline). Given the heterogeneity of reporting of hypoglycaemia and weight outcomes in clinical trials, some assumptions were necessary in the health economic modelling. These assumptions were all fully discussed and agreed by the guideline development group as reflective of clinical practice. Where possible, these assumptions were tested using sensitivity analyses. In a step forward from any existing cost–utility analysis modelling, parameters relating to hypoglycaemia and weight were sampled probabilistically. Therefore whilst average results may appear homogenised, the experience of individually modelled people with type 2 diabetes was different.
350	Association of the British Pharmaceutical Industry	Full	13	1.4 figure 1	Specifically, the ABPI is concerned that the 'Algorithm for Blood Glucose Lowering Therapy' guides prescribers to take a restrictive and linear approach that does not consider the holistic needs of NHS patients with type 2 diabetes. The algorithm needs to be changed to recognise the substantial pharmacological and clinical differences between and within classes of therapies, such as DPP-4 inhibitors, GLP-1	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice

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					receptor agonists, SGLT-2 inhibitors and insulin formulations and position them appropriately within the treatment pathway. For NHS patients who are at risk of weight gain or hypoglycaemia, treatment options that promote weight loss or reduced weight gain to minimise additional metabolic disturbances should be chosen in preference after metformin, or when metformin is contraindicated or not tolerated.	around which pharmacological interventions are appropriate for consideration.
358	Association of the British Pharmaceutical Industry	Full	13	1.4 figure 1	**Specific Clinical Concerns** The medicine algorithm does not reflect current clinical guidelines and existing NICE Technology Appraisal guidance for newer agents. This is inconsistent and confusing. The draft positioning of these treatment classes as suitable only when a sulphonylurea is contraindicated is inconsistent with all existing guidance, including current NICE guidance.	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 (liraglutide) and NICE technology appraisal guidance 248 (exenatide prolonged-release). Cross-references have been revised to make clearer how NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. The Technology Appraisal team at NICE will also consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
360	Association of the British Pharmaceutical Industry	Full	13	1.4 figure 1	**Specific Clinical Concerns** The medicine algorithm guideline is inconsistent with both current UK clinical practice, and the position taken by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). The EASD/ADA	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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					positioning statement recognises the need to individualise patient care based on a range of factors beyond glycaemic control (such as weight and risk of hypoglycaemia) in order to achieve the best outcomes for persons with type 2 diabetes[i].	recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
354	Association of the British Pharmaceutical Industry	Full	14	1.4 figure 2	**Specific Clinical Concerns** The draft guideline rightly places emphasis on the holistic care of NHS patients with diabetes including the importance of weight loss and of taking measures to reduce the risk of hypoglycaemia. In contrast the glycaemic-management medicines algorithm encourages preferential use of agents proven to negatively impact these outcomes. Newer branded medicines with positive NICE TA Guidance have demonstrated benefit in both weight loss and glucose dependent glycaemic control; we therefore believe their use should be encouraged in patients with these concerns fully in line with existing NICE TA Guidelines.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate.
355	Association of the British Pharmaceutical Industry	Full	198	38 Table 61 linking evidence	**Specific Clinical Concerns** Current glucose management recommendations within the existing NICE guideline[ii] are well established in UK clinical practice. It is concerning that should the new guideline be implemented, it could drive GPs to consider a less individualised approach to diabetes	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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				to recommendations	management that proposes prescription of medicines that may be clinically inappropriate for some type 2 diabetes patients. In addition, while ABPI supports the use of individualising care for diabetes patients it is important that clinicians are familiar with the use of medicines such that they are able to reflect on both the evidence and their experience of use. As such, the position of repaglinide, having limited UK clinical experience is over prominent.	The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
357	Association of the British Pharmaceutical Industry	Full	20	33 to 38	**Specific Clinical Concerns** The algorithm as proposed is likely to result in a less individualised care plan for patients. For example, repaglinide[iii] must be given three times daily,[iv] a recognised factor in poor medicines adherence. What is more, patients are more likely to be switched through several treatment regimens as no other treatments can be added to repaglinide. It is recognised that some of the medicines positioned within the algorithm remain valid treatment options in particular patients, but they are not suitable for inclusion in a "one-size-fits-all" algorithm. The algorithm as proposed is likely to result in a less individualised care plan for patients.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. In particular, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are

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						appropriate, choose the option with the lowest acquisition cost).
356	Association of the British Pharmaceutical Industry	Full	20	39 to 41	**Specific Clinical Concerns** The algorithm proposes some medicines which, in their approved SmPC labelling are variously cautioned or noted as having undesirable effects of weight gain (thiazolidinediones, rapid acting insulin secretagogues) and hypoglycaemia (rapid acting insulin secretagogues). To exemplify the complexity of individualisation of care, the case of pioglitazone is particularly relevant when liability for cardiovascular events is considered.[v] Use of pioglitazone in diabetes care has these well described characteristics and its use should be guided by the warnings and precautions around fracture risk, weight gain and worsening of severe heart failure, i.e. based upon the specific needs and risk factors of the individual patient. [vi]	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
361	Association of the British	Full	250	29	**Specific Clinical Concerns** Also, as it currently stands, there is a mismatch with the stopping rules and new glycaemic	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules

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	Pharmaceutical Industry			-37	targets where a GLP-1 receptor agonists is used in conjunction with an insulin. Insulin is known to cause weight gain while GLP-1s are associated with weight loss, the net effect of which is likely to offset in total or in part any incremental weight benefit of GLP-1 therapy. This would therefore make the current target for continuing on a GLP-1 unachievable (1 per cent drop in HbA1c and 3 per cent reduction in BMI). Further, the draft guideline does not recognise current widespread use of GLP-1s in conjunction with basal Insulin in UK clinical practice[vii] and may restrict this practice if it can only take place in a "specialist care setting". The guidelines should be clear in defining what constitutes a "specialist care setting" with a greater emphasis on the expertise of the prescriber rather than the physical setting.	that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances. The guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
344	Association of the British Pharmaceutical Industry	Full	General	General	The Association of the British Pharmaceutical Industry (ABPI) welcomes the opportunity to respond to the Draft NICE Type 2 diabetes guidelines.	Thank you for your feedback.
345	Association of the	Full	General	General	On 7 January 2015, the National Institute for Health and Care Excellence (NICE) issued a	Thank you for your feedback. The guideline development group has reflected on the clinical

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	British Pharmaceutical Industry				draft clinical guideline on the management of type 2 diabetes by the NHS in England and Wales. The ABPI agrees overall with many elements of the draft guideline including the need for patient-centred care; the importance of weight loss and dietary management; and recognition of the detrimental impact of hypoglycaemia on a patients' quality of life. However, we share the concerns of the diabetes community that the section on 'Blood Glucose Management' is fundamentally flawed. The ABPI is disappointed with the recommendations in the 'Blood glucose management' section of the guideline and requests that NICE revises this section, including the glucose-management medicine algorithms.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
346	Association of the British Pharmaceutical Industry	Full	General	General	The ABPI believes that the guideline is potentially too heavily focused on achieving short-term cost efficiencies, at the expense of individualised patient care. It appears fundamentally inconsistent with NHS England and the Department of Health's medicines optimisation agenda and runs counter to NICE's own guidance and focus on promoting high quality care within the NHS. Given the commitments from NHS England to support the	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets

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					uptake of innovation, we find it surprising that the draft guideline does not include the latest NICE reviewed medicines that have been subject to NICE technology appraisal. The apparent focus on crude drug acquisition costs will set back NHS clinical practice.	this guideline apart from other internationally recognised guidelines. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate.
347	Association of the British Pharmaceutical Industry	Full	General	General	The draft guideline not reflect current NICE's own Single Technology Appraisals Guidance (TA315, TA151, TA288, TA248, TA53, TA203, TA60, TA274, TA301), nor does it evaluate the newer diabetes medicines have not been through NICE TA review. It also runs counter to the patient-centric approach of the well-established and respected joint guideline recently issued by the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA), as well as common and established clinical practice in the UK.	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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						in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. This guideline updates and replaces NICE technology appraisal guidance 203 (liraglutide) and NICE technology appraisal guidance 248 (exenatide prolonged-release).
348	Association of the British Pharmaceutical Industry	Full	General	General	ABPI calls on NICE to fundamentally revise the glucose-management medicine algorithm detailed in the draft NICE type 2 diabetes clinical guideline so that it clearly supports clinicians to deliver an individualised patient-centred care approach to type 2 diabetes management for NHS patients fully in line with the requirements of medicines optimisation.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been

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						simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
351	Association of the British Pharmaceutical Industry	Full	General	General	The guideline does not reflect the principles and opportunity to improve patient care set out within the Pharmaceutical Price Regulation Scheme 2014 (PPRS) agreement between the UK Government and the pharmaceutical industry; specifically '*1.4.3 to improve access to innovative medicines commensurate with the outcomes they offer patients by ensuring that medicines approved by NICE are available widely in the NHS*'[viii]. If implemented, the draft algorithms would discourage and delay the use of innovative, cost-effective medicines which the NHS – including the Department of Health, NICE and NHS England – has done so much to embed within clinical practice over the last four years through the Innovation, Health and Wealth programme and now enshrined within the NHS *Five Year Forward View*.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
352	Association of the British Pharmaceutical Industry	Full	General	General	One of the core stated aims of the NHS *Five Year Forward View* is to accelerate useful health innovation: '*we are committed to accelerating the quicker adoption of cost-effective innovation – both medicines and medtech*'[ix]. Furthermore, the PPRS agreement presents the	Thank you for your feedback.

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					NHS with a unique opportunity to increase the availability and use of the best branded medicines. It allows clinicians to have greater flexibility to prescribe newer, more innovative medicines, because all of the costs of prescribing branded medicines over agreed levels are underwritten by the pharmaceutical industry.	
353	Association of the British Pharmaceutical Industry	Full	General	General	The recent Diabetes UK State of the Nation 2014 report[x] highlights that 80 per cent of the £10 billion of NHS annual spend on diabetes is spent on managing complications, most of which could be prevented. The same report outlines the continuing issue of NHS patients failing to achieve treatment targets and calls for performance improvements to be made. The guideline should seek to support such progress, not undermine it through the recommendation of a prominent position for medicines that induce weight gain further increasing insulin resistance and metabolic complications.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
359	Association of the British Pharmaceutical Industry	Full	General	General	**Specific Clinical Concerns** The guideline should recognise the pharmacological and clinical differences based on the evidence available to support use, between and within classes of therapies, such as GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors and insulin formulations. Further, it should encourage healthcare	Thank you for your feedback. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of

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					professionals to consider these in their individualised approach to therapy. This would then be in line with the medicines optimisation principles as set out by the Royal Pharmaceutical Society in 'Medicines Optimisation: helping patients to make the most of medicines'[xi].	drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). GLP-1 mimetics are recommended at second intensification. Based on the updated evidence review and health economic analysis, the guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria

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						and stopping rules from the previous iteration of the guideline, CG87. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
362	Association of the British Pharmaceutical Industry	Full	General	General	ABPI calls for NICE to fundamentally revise the glucose-management medicine algorithm detailed in the draft NICE type 2 diabetes clinical guideline. The algorithm must clearly support clinicians to deliver an individualised patient-centred care approach to type 2 diabetes management.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
543	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based 1. *Placebo controlled trials (at first and second intensification stage) were excluded from the systematic review and NMA informing the guideline*	Thank you for your feedback. As explained in section 8.4.1.4 (full guideline), the guideline development group agreed to concentrate on evidence that was of direct relevance to the individual decision problems under consideration. It is incorrect to state that the

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					<u>Evidence</u> The purpose of any network meta-analysis (NMA) is to include both direct and indirect evidence. The GDG approach ignores all indirect evidence via placebo for the intensification networks. e.g. all oral anti-diabetic (OAD) + metformin (MET) versus placebo + MET trials would not be included in the first intensification network, ignoring a substantial portion of the evidence. The exclusion of placebo controlled trials contradicts NICE's own guidance in this matter (see TSD1 Introduction to evidence synthesis for decision makers http://www.nicedsu.org.uk/evidence-synthesis-tsd-series%282391675%29.htm) Page 4, *"Criteria for inclusion of treatments are described (Section 3), distinguishing between the comparator set of treatments in the decision analysis, and the comparator set of treatments used in synthesis. Once a target patient population has been defined, a suggested trial inclusion rule that avoids potential ambiguity regarding the relevance of evidence is to include any trial that compares at least two treatments in the synthesis comparator*	exclusion of trials comparing 1 or more treatments in combination with placebo with 2 or more treatments contravened the DSU TSD. All trials that compared at least 2 treatments in each decision problem were included, as recommended. Combinations including placebo were not part of the decision problem. A separate question arises as to whether the inclusion of such evidence within the network meta-analyses would have enhanced precision in estimates of effect for the regimens of interest (referred to by TSD as broadening the 'synthesis set' beyond the 'decision set'). Such an approach might have allowed more precise estimates to be made, though it is also possible that increased clinical heterogeneity would have introduced unhelpful statistical inconsistency into the models. It should also be noted that other sources of additional indirect evidence beyond the decision set exist – for example, a large amount of evidence comparing regimens that are currently unlicensed in this country, most notably those containing rosiglitazone. The guideline development group and developers took the decision not to extend the network to include any evidence of only indirect value, as coherent networks were generally possible relying on directly relevant trials alone.

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					set". <u>Clinical implication</u> We believe that this represents an important omission of data sources as data from placebo controlled trials could have been qualitatively summarised to provide the guideline development group with a highly relevant set of broader clinical data (beyond the four critical outcomes included in the NMA) to inform the treatment algorithm, and to ensure that it was aligned with an individualised, patient-centred care approach recognising the differences in tolerability profiles within and between treatment classes. This is particularly important when we consider that the results of the NMA informing the draft guideline do not demonstrate clinically meaningful differences between treatments in the key outcome of glycated haemoglobin (HbA1c). For example, if we consider a comparison of the HbA1c NMA data for MET+ pioglitazone (PIO) versus MET+ sulfonylurea (SU) versus MET+ dipeptidyl peptidase 4 (DPP4) at first intensification (a segment of the treatment algorithm likely to affect the majority of patients with type 2 diabetes), table 63, page 97 in appendix J shows no statistically significant differences between these treatment regimens for HbA1c at 12 months demonstrating that	

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					none of the combinations are superior to any other in terms of glycaemic control, and showing the need for a more flexible algorithm, which supports clinicians to deliver an individualised "patient-centred care" approach to type 2 diabetes management. Recommendations Relevant data from placebo controlled trials should be considered by the GDG to inform a revised, individualised "patient centred care" approach to the algorithm.	
544	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based 2. *The systematic reviews of the evidence focused on four key outcomes with limited consideration of other clinically relevant outcomes* Evidence The systematic review of the randomised controlled trial (RCT) evidence did not consider treatment-specific or serious adverse events, which may be associated with significant cost implications for the NHS. These outcomes were not extracted from the included trials with only four key outcomes being extracted and included in the NMA and subsequent economic modelling (HbA1C, hypoglycaemia, adverse events, and change in body weight). Whilst we recognise that treatment-specific adverse events are	Thank you for your feedback. NICE guidance is not intended to supplant Medicines and Healthcare products Regulatory Agency (MHRA) oversight of prescribed medication; when discussing treatment options with patients, individual prescribers are expected to be familiar with each product's summary of product characteristics and other relevant national guidance. This is important, both to ensure that prescribers have access to the fullest possible safety information and to 'future-proof' NICE guidance against the emergence of evidence on rare harms as experience with each product is accumulated. The focus of the network meta-analyses and health economic modelling was on the outcomes that are relevant to all patients taking antihyperglycaemic medication. The guideline development group (GDG) acknowledges that, in the individual

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					seldom suitable for inclusion in a NMA as each treatment and class will have a different tolerability profile, we think that data extraction of these outcomes (and direct meta-analysis where feasible) would have provided the GDG with highly relevant data to inform the treatment algorithm and to ensure that it was aligned with an individualised, patient-centred care approach. Whilst we agree with the objective of the separate systematic review carried out to provide supplementary information on the long-term serious adverse events of pharmacological treatments for diabetes, we consider the methods used to be significantly limited. The review presented in section 8.5 used narrow inclusion criteria resulting in the inclusion of only five studies for a limited number of treatments. Significantly, no studies for pioglitazone (a treatment with SPC cautions as described in comment 1 above) were included. The narrow inclusion criteria of this review contradict current European Medicines Agency (EMA) guidance to assess safety data using the complete development program in order to utilise all available data to detect potential signals suggesting an increased risk for cardiovascular (CV) or other uncommon adverse events (Section 4.4.3, CHMP Guideline on clinical investigation of medicinal products in	circumstances of particular cases, other outcomes – especially those related to the safety of the medicines – will be of relevance to the prescribing conversation. Because of the limited amount of evidence that was identified in the long-term safety systematic review (section 8.5, full guideline) and to prevent duplication of existing work, the GDG agreed to cross refer to the MHRA which considers all available evidence including those from databases and registries. In the Linking Evidence to Recommendations table (section 8.5.4, full guideline), the GDG acknowledged that the PROActive trial on pioglitazone was excluded but agreed that long-term serious adverse effects are identified in the MHRA safety alerts. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					the treatment or prevention of diabetes mellitus, 2012). Clinical Implication It is clear from the recent ADA/EASD position statement, which strongly advocates a patient-centred approach, that multiple factors beyond glucose-lowering effects should be considered when choosing the most appropriate treatment strategy for a person with type 2 diabetes (Inzucchi et al, 2015). Table 1 in the position statement includes a range of properties of glucose-lowering agents that may guide individualised treatment choices in patients with type 2 diabetes, which extends far beyond the four outcomes considered within the systematic review that informed the development of this draft guideline. For example, the profile of treatments regarding gastrointestinal (GI) side effects, fractures, heart failure, cardiovascular disease (CVD) event and lipid profiles is summarised in table 1. Recommendation The GDG should consider relevant data regarding a broader set of outcomes to inform a revised, individualised, "patient centred care" approach to the algorithm. References Inzucchi S.E. et al. Management of	

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					Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015 38:1(140-149)	
545	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based 3. *The NMA inappropriately pooled together different patient populations (drug naive and prior drug populations) at first intensification stage.* Evidence For first intensification of treatment, sensitivity analyses were undertaken on the typical population for this phase of treatment, that is, people who were previously on one oral antidiabetic medicine, including those whose medication had failed to adequately control blood glucose levels. No major differences were observed in the direction of effect for changes in HbA1c and hypoglycaemia, between people on one oral antidiabetic medicine and the full population which included studies of mixed populations of people who were drug naïve, or on one or more oral anti-diabetic medicines at screening (see Appendix J). Therefore, the full analyses were used and reported in section 8.4.8.2.	Thank you for your feedback. As recognised in your feedback, the guideline development group (GDG) and developers were concerned that the issues discussed here could potentially have an impact on the applicability of the full evidence base to the clinical decision problems. It was for this reason that sensitivity analyses were undertaken to explore the possibility that effects were different in populations that were most closely representative of the patients to whom recommendations would apply (section 8.4.2, full guideline). In doing so, no evidence of systematic variability between the full dataset and the more tightly defined subgroup was identified. Although, this was necessarily a subjective judgement, the GDG agreed that there was no evidence of systematic variability. In your feedback, there is no cited discrepancies between the evidence-bases that are apparent in this comparison, nor any additional evidence to support the suggestion that effects are likely to be different. In the absence of evidence – either in our analysis that directly explored this concern or in your feedback – that this theoretical risk had any material effects on the analysis, it is

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					This goes against NICE's own methodology recommendation: See NICE DSU TSD1: Introduction to Evidence Synthesis for Decision Making Page 10-11 ….http://www.nicedsu.org.uk/evidence-synthesis-tsd-series%282391675%29.htm *"Synthesis of evidence from clinically heterogeneous populations, not only increases the risk of statistical heterogeneity and inconsistency, but often requires highly implausible assumptions, such as assuming that interventions are equally effective in a naïve population or in a population that has already failed on that intervention or has contra-indications to its use".* Furthermore, the justification for using a mixed population is based on the lack of 'major' differences in direction of effect which is vague and subjective. We rather believe that this approach might have resulted in flawed outcomes as there is a strong clinical rationale to split out treatment naive and prior drug populations. There are likely to be differences in duration and stage of disease between these patient groups; and prior drug patients typically represent a more difficult to treat population. Recommendation The GDG should review the analyses split by	reasonable for the GDG to conclude that reliance on the fuller dataset, with the increased precision it provides, was the most appropriate course of action.

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					population to ensure that there are no differences in outcomes per population.	
546	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based *4. The sequence in which medicines are used in the economic model does not reflect standard clinical practice.* Evidence The review question "Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?" was split into several sub-questions which appear to have been answered in isolation to one another. Health economic evidence for the choice of initial therapy is based on the assumption that whatever treatment patients receive at this point is followed by metformin + sulphonylurea and then metformin + insulin isophane (NPH Insulin). This is not likely to be the case in clinical practice. This modelling assumption homogenises the differences between treatment options, so that the Quality-adjusted Life Year (QALY) differences are very similar between treatments and the model then becomes driven by drug acquisition cost. For example, in the first intensification model, treatment only varies by choice of the first	Thank you for your feedback. The guideline development group considered that the modelled sequence of treatments reflected clinical practice. Alternative sequences were modelled and found not to influence the results (appendix F 4.13). The guideline development group considered that modelling intensification was more realistic than not modelling intensification, as was modelled in a number of included cost–utility analyses (CUAs). In the health economic model, treatment intensification was driven by HbA1c treatment effect and pathway. In a step forward from any existing CUA modelling, both of these were sampling probabilistically. Therefore whilst average results may appear homogenised, the experience of individually modelled people with type 2 diabetes was very different. The economic model outputs were compared to existing CUAs in appendix F 5.3

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					intensification drug where the sequence is [First intensification drug] then Metformin-NPH insulin: • Patients spent on average 3.7 years (Appendix F, page 146) on their first intensification drug in the model. • The mean patient life years covered by the model was ~16.3 years (Appendix F, Table 120). • Hence the majority of the model cycles cover the period after discontinuation of the first intensification drug. • Appendix F, Table 121 in the economic model report shows the mean lifetime QALYs by choice of first intensification drug. The differences in QALYs between comparators are small. o The best average QALY gain is 8.286 years for metformin + liraglutide, and the worst QALY gain is 8.217 years for metformin + piolglitazone. The difference between the best and worst QALY on average is 0.069 years = 3.6 weeks • Appendix F, Table 122: The difference in lifetime costs is small for most of the comparators (except for GLP1s): o E.g. Cost of met + SU – cost of metformin + pio = £20653-£20525 = £128	

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					Recommendation The GDG should consider a comparison of the economic model outputs with outputs from other diabetes models, which have taken a different approach to treatment sequencing, which is more reflective of clinical practice.	
547	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based 5. *The economic model is significantly limited in its approach to the effects of treatments on body weight* a) The economic model chosen, the UK Prospective Diabetes Study 01 (UKPDS01) model, was not designed to incorporate the effects of treatments on weight. The model was originally developed in the 1990s when new treatments with the benefits of weight loss and blood pressure reduction were not available. Since that time, several models, which include a weight component, have been developed and independently validated. Rather than use one of these newer models, the modelling group used the UKPDS01 model with a 'bolt on' function to account for weight, and did not validate the results of the economic modelling using any of the other peer-reviewed	Thank you for your feedback. Due to the fully probabilistic structure of the health economic model, no other existing type 2 diabetes model was able to adequately validate the approach taken. The application of utility changes to both weight gain and loss was clearly described in appendix F 3.10.3. The guideline development group considered alternative assumptions regarding treatment-related weight change profiles and chose to assume treatment-related weight loss would only be sustained for 1 year (see appendix F 3.2.6). This assumption was tested in sensitivity analyses (see appendix F 3.11.2.2).

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					and validated models, which include a weight change component, such as the Centre for Outcomes Research Diabetes Model (CDM). Without validation using an alternative model, the confidence in the outputs of the modelling are significantly reduced. b) The economic model only includes a disutility for weight gain. There is no evidence that a utility benefit was applied for weight loss. This would bias against treatments included in the model, such as glucagon-like peptide-1s (GLP1s) with demonstrated weight loss (Phung et al, 2010). c) The economic model only incorporates weight loss at 1 year with the stated rationale that there is no evidence beyond 1 year. However, this is not the case. Two year data is available for several treatments considered within the scope of this guideline. Four year data are available for the SGLT2s, which have received positive TA guidance. For example, there is evidence of weight gain with pioglitazone containing combinations and the NMA showed that pioglitazone-metformin and pioglitazone-sulfonyurea resulted in a	

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					statistically significant increase in weight compared to metformin-sulfonylurea at 24 months (~1kg and ~5kg respectively), whilst all metformin + DPP4 combinations had significantly lower weight compared to metformin-sulfonylurea at 12 (Full version, figure 47, ~ -2kg) and 24 months (Full version, figure 49, ~ -2 to 3 kg). <u>Recommendation</u> The results of the economic modelling should be validated using one of the other peer-reviewed and validated models, which includes a weight change component, such as the Centre for Outcomes Research Diabetes Model (CDM). <u>References</u> Phung et al. Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes. JAMA. 2010;303 (14):1410-1418.	
548	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	<u>Concern: Inflexibility of proposed treatment algorithm is not evidence based</u> 6. <u>*The economic model does not seem stable and there are limitations and potential errors in model inputs*</u> a) <u>The health economic model does not seem stable</u> as there are examples	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological

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					where the results indicate some dominant treatments. This is not the impression from the NMA as few results are statistically significant or clinically important according to the minimal difference. For example, in the initial therapy model, metformin is the most effective treatment and completely dominates all other treatments. While it is plausible that metformin may be cost-effective, even the GDG acknowledge that metformin is not the most effective treatment (in terms of HbA1c control) and it is strange that it dominates all other treatment options for every plausible range of input values. b) A lower drug acquisition cost (compared to alternative treatments considered) results in repaglinide being the second most cost-effective treatment in the initial therapy economic model. However, in practice, this cost saving could be offset, in part or in totality, by the resource use required to switch a patient off repaglinide in actual practice requiring two new drugs to be introduced in sequence, which has not been considered in the model. Appendix F, Table 87 shows the cost of treatment switches for initial therapy. Repaglinide	management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations. Metformin was dominant due to a combination of superior lifetime discounted treatment costs and superior weight and hypoglycaemia effects, QALYs and costs rather than HbA1c effects alone (see disaggregated cost and QALY results in appendix F 4.1). Treatment switch costs shown in appendix F table 87 related to treatment switches due to intolerance, rather than intensification (see appendix F 3.9.2). Like virtually all existing models, the health economic model had annual cycles and was not structured to consider short term deterioration in control that could occur when switching or intensifying treatment options. There were not errors in the model inputs. Differences between treatments were reduced due to the impact of therapy intensifications, with less effective (HbA1c) therapies intensifying

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					inaccurately has the lowest cost of £6 on average compared to £9 for pioglitazone. There would also be a delay before treatment could be intensified, during which glucose levels would be inadequately controlled. This does not appear to have been considered in the model. Given the uncertainty in the economic modelling and that it is unlikely that patients and clinicians would find the inevitable treatment switch acceptable, this large change in practice does not seem viable. c) <u>There appear to be errors in the model inputs:</u> • Appendix F, Table 56: The model input for hypoglycaemia rates for repaglinide (0.674) is approximately four times that for sitagliptin (0.160). In table 86, however, the disutility for symptomatic hypoglycaemia for repaglinide and sitagliptin are estimated to be similar (-0.256 & -0.254), as are the mean lifetime costs associated with severe hypoglycaemia; £707 for repaglinide and £715 for	sooner (see appendix F table 84 – placebo has the lowest hypoglycaemia rate but the highest QALY loss from hypoglycaemia as placebo intensified to therapies with higher hypoglycaemia rates fastest). The inability of the health economic model to include all the comparators was noted as a limitation (appendix F 5.2.1). However, this analysis included more comparators than any previous analysis.

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					sitagliptin. • The economic model inputs indicate that weight gain is worse for metformin+pioglitazone (+1.907) than metformin + sulfonylurea (+1.354), but the weight-associated disutility output is worse for metformin + sulfonylurea (-0.377) than metformin+pioglitazone (-0.363) (Appendix F Table 57 & 121). d) <u>The economic model only included treatments with results from the NMA for all four outcomes at 12 months, which significantly decreased the number of treatments assessed by the model</u>. For the initial therapy model, 7 of 12 treatments were included in the model. Acarbose, metformin modified release, sulfonylurea modified release, linagliptin and saxagliptin were excluded. The first intensification model excluded 7 of 14 treatment combinations. <u>Recommendation</u> These concerns should be assessed with changes incorporated in the modelling. Recommendations should then be revised in light of any changes in modelling outputs.	

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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549	AstraZeneca UK	Full Full	13 -15 255	Algorithm (Figures 1,2, 3) 21-24	<u>Concern: Prominent and rigid recommendation for metformin + pioglitazone at first intensification</u> The proposed, "one size fits all" treatment algorithm, would result in the vast majority of patients receiving metformin and pioglitazone at first intensification without consideration of important patient characteristics. <u>Clinical Implication</u> Pioglitazone is associated with weight gain, fractures, oedema, and worsening of heart failure (Pioglitazone SPC); and is therefore not commonly used in the UK. These adverse reactions are of particular concern in the elderly; and the SPC for pioglitazone states that in light of age-related risks including fractures and heart failure, the balance of benefits and risks should be considered carefully both before and during treatment in the elderly. It is clear that the GDG discussed these cautions for pioglitazone (page 221, full guideline) yet these have not followed through into the recommendations; and are not reflected by the rigid treatment algorithm. We are concerned that the inflexible	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

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					recommendation for pioglitazone as the primary drug for first intensification with no reference to the cautions in the SPC could lead to inappropriate use of pioglitazone and poorer outcomes for patients. <u>Recommendation</u> Revise the treatment algorithm to include clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised "patient-centred care" approach rather than contraindications alone determining drug choice.	
550	AstraZeneca UK	Full Full	13 -15 255	Algorithm Figures 1,2,3 4-8	<u>Concern: Prominent recommendation for repaglinide as initial therapy</u> Repaglinide, a treatment associated with an increased risk of weight gain and hypoglycaemia with a three times daily dosing regimen (Phung et al, Repaglinide SPC) has been recommended as initial therapy for those patients contraindicated or intolerant to metformin. <u>Clinical Implication</u> The three times daily dosing regimen will pose a significant challenge for patients who struggle to adhere and comply with their medicine regimen (Guillausseau PJ et al, 2003). Once daily	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The guideline development group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The algorithm

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					treatment regimens offer a clinically significant benefit for some patients. Increased adherence may result in greater glycaemic control, and in turn, improve outcomes and lower health care usage and costs (Currie et al, 2012; Lau et al, 2004). Recommendation Revise the treatment algorithm to include clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised "patient-centred care" approach rather than contraindications alone determining drug choice. References Currie CJ et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. Diabetes Care. 2012 Jun;35(6):1279-84. doi: 10.2337/dc11-1277. Guillausseau PJ. Influence of oral antidiabetic drugs compliance on metabolic control in type 2 diabetes. A survey in general practice. Diabetes Metab 2003, 29.79-81 Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent	has been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

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					hospitalization among individuals with type 2 diabetes. Diabetes Care. 2004 Sep;27(9):2149-53. Phung et al. Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes. JAMA. 2010;303 (14):1410-1418.	
551	AstraZeneca UK	Full Full	13 -15 255	Algorithm Figures 1,2,3 25-26	<u>Concern: Rigid recommendation for metformin plus sulfonylurea without offering other treatments for patients at high risk of hypoglycaemia</u> Metformin plus sulfonylurea is recommended at first intensification for all patients for whom pioglitazone is contraindicated or not tolerated with no reference to other treatment options for patients at significant risk of hypoglycaemia. <u>Evidence</u> NMAs have demonstrated that the DPP4 inhibitor and SGLT2i classes have a lower risk of hypoglycaemia (as add-on to metformin) compared to sulfonylurea. Figure 39, page 209 of the full guideline shows that metformin-sitagliptin, metformin-saxagliptin, and metformin-linagliptin combinations at first intensification have a significantly lower risk of hypoglycaemia (annual incidence) compared to metformin-sulfonylurea. A recently published NMA	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

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					comparing dapagliflozin with other diabetes medications in combination with metformin found that dapagliflozin resulted in a significantly lower hypoglycaemia risk versus sulfonylurea (OR: 0.05 [0.01, 0.19]) over 52-weeks (Barnett et al, 2014). <u>Clinical Implication</u> Hypoglycaemia is an important side effect of many anti-diabetic medications and contributes to the overall morbidity associated with the disease (Frier et al, 2014; Nirantharakumar et al, 2012; Turchin et al, 2009). The rigid recommendation to use a sulfonylurea (a treatment class associated with hypoglycaemia) without offering other treatments for patients with high risk of hypoglycaemia could lead to poorer patient outcomes. <u>Recommendation</u> Revise the treatment algorithm: • To include clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised, "patient-centred care" approach rather than contraindications alone determining drug choice.	

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					• To clearly incorporate the positive SGLT2i NICE TA guidance at first intensification (add-on to metformin) if there is a significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated <u>References</u> Barnett et al, Systematic Review and Network Meta-analysis to Compare Dapagliflozin with other Diabetes Medications in Combination with Metformin for Adults with Type 2 Diabetes, 2014, Intern Med S6: S6-006 Frier, B. M. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications Nat. Rev. Endocrinol. 10, 711–722 (2014) doi:10.1038/nrendo.2014.170 Nirantharakumar K et al, Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. Diabet Med 2012; 29: e445–448. Turchin A et al, Hypoglycaemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care 2009; 32: 1153–1157.	
552	AstraZeneca UK	Full	13	Algorithm	<u>Concern: The algorithm does not encourage weight loss early on and lacks a clear position</u>	Thank you for your feedback. The guideline development group has reflected on the clinical

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			-15	Figures 1,2,3	<u>for the SGLT2i class with demonstrated weight loss and positive NICE TA guidance.</u> There is a disconnect between recommendations 11 and 12 advising health care professionals to provide patients with advice emphasizing weight management and the proposed treatment algorithm. The algorithm prominently and inflexibly positions pioglitazone, sulfonylurea and repaglinide, treatments which may induce weight gain early on in the pathway; and lacks a clear position for the SGLT2i class for which weight loss has been demonstrated. While reference is made to the SGLT2i NICE TAs, the class has been deemed to be out of scope. This lack of alignment between the draft guideline and existing TA guidance is not in keeping with NICE process, and will lead to significant confusion for HCPs. The NICE guidelines manual states that when a guideline and TA guidance are developed concurrently, which is likely in this case regarding the SGLT2i NICE TAs, the final recommendations in the guideline and the appraisal should be complementary and consistent (page 155, Developing NICE guidelines: the manual, October 2014). The manual also states that "when recommendations from a published technology appraisal are	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).The guideline also reinforces

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					incorporated into a new guideline, they should usually be reproduced unchanged (verbatim)" (page 152). Evidence There is evidence demonstrating the benefit of weight loss following treatment with the SGLT2i class, which informed the positive TA guidance for dapagliflozin and canagliflozin (TA288, TA315). For example, a head to head randomised controlled trial demonstrated sustained and stable weight loss with dapagliflozin (add onto metformin) versus weight gain with glipizide (add onto metfomin) at 208 weeks (−3.95 vs +1.12 kg): difference of −5.07 kg (95% CI: −6.21, −3.93) (Langkilde et al, 2013). Data from a NMA comparing dapagliflozin with other diabetes medications in combination with metformin demonstrates significant reductions in weight by 24-weeks for dapagliflozin versus DPP-4i (-2.24 kg [95% CI -3.25,-1.24]) and thiazolidinediones (TZDs) (-4.65 kg [-5.89,-3.45]), and at 52-weeks versus SUs, DPP-4i and TZDs (Barnett et al, 2014). Clinical Implication Currently, 90% of adults with type 2 diabetes are overweight or obese (Public Health England, 2014) with weight being a significant aggravating factor for deterioration in diabetes (Glogner et al, 2014). We are concerned that the	the importance of diet and lifestyle interventnions throughout the care pathway. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.

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					proposed algorithm, which does not encourage weight loss early on may lead to a decline in outcomes for overweight patients. <u>Recommendation</u> Revise the treatment algorithm to: • Include clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised, "patient-centred care" approach rather than contraindications alone determining drug choice • Clearly incorporate the positive SGLT2i NICE TA guidance at first intensification (add onto metformin) if there is a significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated <u>References</u> Barnett et al, Systematic Review and Network Meta-analysis to Compare Dapagliflozin with other Diabetes Medications in Combination with Metformin for Adults with Type 2 Diabetes, 2014, Intern Med S6: S6-006 Langkilde, M.A. Nauck, S. Del Prato, S. Durán-	

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					Garcia4, K. Rohwedder,Theuerkauf, S.J. Parikh. Durability of dapagliflozin vs glipizide as add-on therapies in type 2 diabetes inadequately controlled on metformin: 4-year data Diabetologia (2013) 56:[Suppl1]S1–S566 . Glogner S et al. The association between BMI and hospitalization for heart failure in 83,021 persons with Type 2 diabetes: a population-based study from the Swedish National Diabetes Registry. Diabet Med. 2014 May;31(5):586-94. doi: 10.1111/dme.12340 Public Health England, 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf	
542	AstraZeneca UK	Full	13 -15	Algorithm (Figures 1,2, 3)	Concern: Inflexibility of proposed treatment algorithm is not evidence based Evidence The recommended treatment sequence appears to be based solely upon the ranking of the outputs from the cost-effectiveness model yet these outputs should be interpreted with caution due to the following methodological limitations concerning both the clinical and cost effectiveness data (described in separate comments below in more detail): 1. The technical team did not include certain data, which could have better	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of

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					informed the guideline recommendations: • Placebo controlled trials (at first and second intensification) including key regulatory trials were excluded • Data extraction from included trials was limited to four key outcomes, so that data from several other key outcomes including serious adverse events and specific treatment-related adverse events were not assessed 2. The NMA inappropriately pooled together different patient populations at first intensification stage. The outputs of the NMA may therefore be flawed. 3. The economic model has several limitations, as stressed by the technical modelling group in their report: "*The results shown here for the original health economic analysis should not be taken as justification for the use or recommendation [of] any of the treatments listed."* This statement from the technical modelling team implies that the outputs of the health economic model are not a sound basis to recommend any single treatment over another. 4. The ranking of the cost-effectiveness	drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). With respect to bullet points: 1 (placebo-controlled trials). As explained in section 8.4.1.4 (full guideline), the guideline development group agreed to concentrate on evidence that was of direct relevance to the individual decision problems under consideration. It is incorrect to state that the exclusion of trials comparing 1 or more treatments in combination with placebo with 2 or more treatments contravened the DSU TSD. All trials that compared at least 2 treatments in each decision problem were included, as recommended. Combinations including placebo were not part of the decision problem. A separate question arises as to whether the inclusion of such evidence within the network meta-analyses would have enhanced precision in estimates of effect for the regimens of interest (referred to by TSD as broadening the 'synthesis set' beyond the 'decision set'). Such an approach might have allowed more precise estimates to be made, though it is also possible that increased clinical heterogeneity would have introduced

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					results is based on the results of a probabilistic sensitivity analysis (PSA), which means that the treatments are ranked by their likelihood of being the most cost-effective treatment option. For example, at first intensification metformin-pioglitazone had a 48% chance of being the most cost-effective; and this implies that there is a 52% chance that it is NOT the most cost-effective. At first intensification, the results should rather be interpreted as showing that none of the metformin treatment combinations are significantly more cost effective than any other. Whilst the draft guideline refers to the "potentially serious limitations" of the economic model (page 220, line 25, full guideline), there is no evidence that these limitations were sufficiently considered by the GDG in arriving at their recommendations. Clinical Implication The treatment algorithm opposes established clinical practice, which tailors drug therapy according to individual patient characteristics (such as weight, age and risk of hypoglycaemia). It guides prescribers to take a restrictive and linear approach for the 85% of type 2 diabetes patients requiring	unhelpful statistical inconsistency into the models. It should also be noted that other sources of additional indirect evidence beyond the decision set exist – for example, a large amount of evidence comparing regimens that are currently unlicensed in this country, most notably those containing rosiglitazone. The guideline development group and developers took the decision not to extend the network to include any evidence of only indirect value, as coherent networks were generally possible relying on directly relevant trials alone. 1 (4 key outcomes). NICE guidance is not intended to supplant Medicines and Healthcare products Regulatory Agency (MHRA) oversight of prescribed medication; when discussing treatment options with patients, individual prescribers are expected to be familiar with each product's summary of product characteristics and other relevant national guidance. This is important, both to ensure that prescribers have access to the fullest possible safety information and to 'future-proof' NICE guidance against the emergence of evidence on rare harms as experience with each product is accumulated. The focus of the network meta-analyses and health economic modelling was on the outcomes that are relevant to all patients taking antihyperglycaemic medication. The guideline development group (GDG) acknowledges that, in the individual circumstances of particular cases,

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					pharmacological treatment, who are able to tolerate metformin (page 28, line 9-11, full version of draft guideline) that does not consider the holistic needs of individuals with type 2 diabetes. The proposed algorithm therefore contradicts a key goal within the guideline: recommendation 1 ("Adopt an individualised approach to diabetes care that is tailored to the person's needs and circumstances, taking into account their personal preferences, comorbidities, risks of polypharmacy, and their ability to benefit from long-term interventions due to reduced life expectancy..."). <u>Recommendation</u> Revise the treatment algorithm to include clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised "patient-centred care" approach rather than contraindications alone determining drug choice.	other outcomes – especially those related to the safety of the medicines – will be of relevance to the prescribing conversation. Because of the limited amount of evidence that was identified in the long-term safety systematic review and to prevent duplication of existing work, the GDG agreed to cross refer to the MHRA which considers all available evidence including those from databases and registries. 2. The GDG and developers were concerned that the issues discussed here could potentially have an impact on the applicability of the full evidence base to the clinical decision problems. It was for this reason that sensitivity analyses were undertaken to explore the possibility that effects were different in populations that were most closely representative of the patients to whom recommendations would apply (section 8.4.2, full guideline). In doing so, no evidence of systematic variability between the full dataset and the more tightly defined subgroup was identified. In the absence of evidence – either in our analysis that directly explored this concern or in your feedback – that this theoretical risk had any material effects on the analysis, it is reasonable for the GDG to conclude that reliance on the fuller dataset, with the increased precision it provides, was the most appropriate course of action.

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						3. The quoted text is taken out of context and refers to comparisons with the previous guideline. Whilst this is stressed in the text, the text has been amended for clarity. 4. The consideration of treatment options as having a given chance of being the most cost-effective needs to take account of the number of treatment options compared. Whilst it is true that metformin-pioglitazone had a 48% chance of being cost effective, there were 6 alternative treatment options. If all 7 treatments had an equal chance of being cost-effective, they would each have a 14% chance. Metformin-pioglitazone showed a much higher probability. The quality assessment of both the original health economic modelling and any existing health economic studies is defined by the NICE guidelines manual (2012) and studies are categorised as having "no limitations", "potentially serious limitations" or "very serious limitations". Studies with "potentially serious limitations" are deemed to have failed 1 or more of the 11 quality criteria. The limitations of the original health economic modelling were outlined in the guideline (8.4.3.7) and fully discussed in appendix F (5.2). Both the original health economic modelling and all included existing health economic studies were

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						found to fall into the "potentially serious limitations" category.
553	AstraZeneca UK	Full Full Full	21 22 13-15	22-24 33-36 Algorithm, Figures 1,2,3	<u>Concern: Choice of DPP-4 inhibitor and GLP-1 should be guided by drug cost</u> AstraZeneca is concerned by the recommendations to choose the DPP-4 inhibitor and the GLP1-mimetic "with the lowest acquisition cost" in recommendations 54 and 60, respectively. <u>Clinical Implication</u> If this clause was maintained in the final guideline, and implemented, HCPs could increase their use of lixisenatide and alogliptin, currently the cheapest GLP-1 and DPP-4, respectively, available in the UK. We are concerned that this change in clinical practice could result in poorer patient outcomes as there are data indicating that the individual GLP-1s achieve different reductions in HbA1C, and hence lowest acquisition cost should not be a criterion for selection. Table 58 in appendix J (results of direct meta-analyses) indicates a higher reduction in HbA1C at 6 months with exenatide twice daily compared	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					with lixisenatide, which is statistically significant (0.17 (95% CI: 0.03, 0.31)). This outcome is based on direct evidence from a single trial (GET-GOAL-X, Rosenstock 2013), which found that lixisenatide was non-inferior to exenatide for the primary outcome of reduction in HbA1c from baseline. However, in its public assessment report for lixisenatide, the European Medicines Agency (EMA) concluded that non-inferiority to exenatide had not been shown robustly. We are also concerned that, to our knowledge, available data for lixisenatide shows that the HbA1C reduction of 1% specified in the guideline as a criterion for continuation of GLP-1 therapy is unlikely to be met. The GetGoal-P and GetGoal-M trials (Ahren et al, 2013; Pinget et al, 2013) found that lixisenatide was more effective than placebo with regard to their primary outcome of reduction in HbA1c from baseline. However, the 0.8–0.9 percentage point mean reductions from baseline in the lixisenatide groups were slightly less than the 1.0 percentage point (11 mmol/mol) reduction specified in NICE guidance as a criterion for continuing GLP-1 treatment beyond six months. In contrast, the DURATION trials for exenatide 2 mg weekly, have demonstrated significant improvements in HbA1c across the spectrum of baseline values, meeting this criteria set by	

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					NICE with change in HbA1c to study endpoint ranging from -1.28% (DURATION 6, Buse et al, 2013) to -1.9% (DURATION 1, Drucker et al, 2008). Regarding the DPP-4 inhibitor class, the draft guideline states that the "GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could....be considered interchangeable" with specific reference that "in a few areas, a case could be made for the superiority of one option over another" (page 223, full guideline). As the GDG was not presented with evidence that suggested that one or more of the options was superior to others across all phases of treatment, it took a decision to refer to the DPP4 inhibitors as a class and inappropriately decided that "a natural extension of this principle" was to encourage prescribers to select the individual DPP-4 inhibitor with the lowest acquisition cost (page 223, full guideline). We note that there are, in fact, important differences between different DPP4 inhibitors regarding their suitability for use in patients with renal failure. It should also be noted that alogliptin was excluded from the guideline scope, so should the GDG wish to retain this contentious recommendation of using the DPP4 inhibitor	

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					with the lowest acquisition cost, then the GDG needs to specifically draw attention to alogliptin being excluded from this recommendation and for the exclusion of alogliptin to be highlighted wherever DPP4 inhibitors are referred to as a class. <u>Recommendation</u> Based on the reasons above, we recommend that the clauses recommending use of the drug with the lowest acquisition cost are removed; and that the differences in clinical profiles within these classes are clearly stated within the key sections of the guideline with an overarching goal of achieving the best outcomes for patients. <u>References</u> Ahren, B., Dimas, A., Miossec, P et al. Efficacy and Safety of Lixisenatide Once-Daily Morning or Evening Injections in Type 2 Diabetes Inadequately Controlled on Metformin (GetGoal-M). Published online before print March 27, 2013, doi: 10.2337/dc12-2006 Diabetes Care September 2013 vol. 36 no. 9 2543-2550 Buse J et al, Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet 2013; 381: 117–24 Drucker D., Buse J., Taylor K., et al.	

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					DURATION-1 study group. Exenatide once-weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, noninferiority study. Lancet, 2008: 372: 1240-50 European Medicines Agency. Lixisenatide European Public Assessment Report (EPAR) Conclusions on the clinical efficacy. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002445/WC500140449.pdf Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab. 2013 Nov;15(11):1000-7. doi: 10.1111/dom.12121 Rosenstock J. Raccah D, Koranyi L et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013 Oct;36(10):2945-51. doi: 10.2337/dc12-2709. Epub 2013 May 22.	
541	AstraZeneca UK	Full	General	General	SUMMARY AstraZeneca agrees with many elements of the	Thank you for your feedback. The guideline development group has reflected on the clinical

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		& NICE			draft guideline concerning the need for patient-centred care, the importance of weight loss, and recognition of the detrimental impact that hypoglycaemia has on patients' quality of life. However, we share the concerns of others in the diabetes community that the section on "Blood Glucose Management" is flawed (O'Hare et al, 2015); does not represent the evidence; and could lead to both a reduction in the quality of clinical care and a negative impact on patient outcomes. The "Algorithm for Blood Glucose Lowering Therapy", opposes established clinical practice and contradicts the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement (Inzucchi et al, 2015), which tailors drug therapy according to individual patient characteristics (such as weight, age and risk of hypoglycaemia). The draft guideline also contradicts its own stated goal for "patient-centred care" as it guides prescribers to take a restrictive and linear approach that does not consider the holistic needs of individuals with type 2 diabetes: 1. The proposed algorithm recommends all patients (without contraindications) receive pioglitazone as add-on to metformin at first intensification 2. Metformin plus sulfonylurea is	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, at first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also

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					recommended at first intensification for all patients for whom pioglitazone is contraindicated or not tolerated with no reference to other treatment options for patients at significant risk of hypoglycaemia 3. Repaglinide as initial therapy is recommended for those patients contraindicated to metformin 4. The guideline lacks a clear position for the sodium-glucose co-transporter 2 (SGLT2) inhibitors in the treatment algorithm. While reference is made to the SGLT2 inhibitors NICE technology appraisals (TAs), the class was out of scope. We are concerned by the clinical implications of these recommendations: • The proposed, "one size fits all" treatment algorithm would result in the vast majority of patients receiving metformin and pioglitazone at first intensification without consideration of important patient characteristics, although pioglitazone is associated with weight gain, fractures, oedema, and worsening of heart failure (Pioglitazone Summary of Product Characteristics [SPC]). The SPC for pioglitazone states that in light of age-related risks including fractures and heart	given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. Regarding the feedback on the clinical and cost effectiveness evidence: 1 (placebo-controlled trials). As explained in section 8.4.1.4 (full guideline), the guideline development group agreed to concentrate on evidence that was of direct relevance to the individual decision problems under consideration. All trials that compared at least 2 treatments in each decision problem were included, as recommended. Combinations including placebo were not part of the decision

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					failure, the balance of benefits and risks should be considered carefully both before and during treatment in the elderly. It is concerning that pioglitazone has been recommended as the primary drug for first intensification, with no reference to the cautions in the SPC. • Hypoglycaemia is an important side effect of many anti-diabetic medications and contributes to the overall morbidity associated with the disease (Frier et al, 2014; Nirantharakumar et al, 2012; Turchin et al, 2009). The rigid recommendation to use a sulfonylurea (a treatment class associated with hypoglycaemia) (Phung et al, 2010) without offering other treatments for patients with high risk of hypoglycaemia could lead to poorer patient outcomes. • Pioglitazone, sulphonylureas and repaglinide, treatments associated with weight gain (Phung et al, 2010), are recommended early on in the treatment algorithm whilst the algorithm lacks a clear position for the SGLT2is, a class for which weight loss has been demonstrated. Currently 90% of adults with type 2 diabetes are overweight or obese (Public Health England, 2014) with weight being a significant aggravating factor for deterioration (Glogner S et al, 2014). We are concerned that the proposed algorithm,	problem. A separate question arises as to whether the inclusion of such evidence within the network meta-analyses would have enhanced precision in estimates of effect for the regimens of interest. Such an approach might have allowed more precise estimates to be made, though it is also possible that increased clinical heterogeneity would have introduced unhelpful statistical inconsistency into the models. It should also be noted that other sources of additional indirect evidence beyond the decision set exist – for example, a large amount of evidence comparing regimens that are currently unlicensed in this country, most notably those containing rosiglitazone. The guideline development group (GDG) and developers took the decision not to extend the network to include any evidence of only indirect value, as coherent networks were generally possible relying on directly relevant trials alone. 1 (inappropriate pooling of populations). The GDG and developers were concerned that the issues discussed here could potentially have an impact on the applicability of the full evidence base to the clinical decision problems. It was for this reason that sensitivity analyses were undertaken to explore the possibility that effects were different in populations that were most closely representative of the patients to whom recommendations would apply (section 8.4.2, full guideline). In doing so, no evidence of

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					which does not encourage weight loss early on, may lead to a decline in outcomes for these patients (Williamson DF, et al 2000). • While reference is made to the SGLT2i NICE TAs, the class has been deemed to be out of scope. This lack of alignment between the draft guideline and existing TA guidance will lead to significant confusion for health care professionals (HCPs). The proposed treatment algorithm is not supported by either the clinical- or cost-effectiveness evidence: 1. The network meta-analysis (NMA) informing the efficacy inputs of the model had several limitations including the exclusion of placebo controlled trials for treatment intensification, and inappropriate pooling of populations. 2. The sequence in which medicines are used in the economic model does not reflect standard clinical practice. 3. The outputs of the health economic (HE) model do not support the rigid treatment sequence in the proposed algorithm. The model outputs should be treated with significant caution by the Guideline Development Group (GDG) when	systematic variability between the full dataset and the more tightly defined subgroup was identified. In the absence of evidence – either in our analysis that directly explored this concern or in your feedback – that this theoretical risk had any material effects on the analysis, it is reasonable for the GDG to conclude that reliance on the fuller dataset, with the increased precision it provides, was the most appropriate course of action. 2 and 3. The guideline development group considered that the modelled sequence of treatments reflected clinical practice. Alternative sequences were modelled and found not to influence the results (appendix F 4.13). The guideline development group considered that modelling intensification was more realistic than not modelling intensification, as was modelled in a number of included cost–utility analyses (CUAs). In the health economic model, treatment intensification was driven by HbA1c treatment effect and pathway. In a step forward from any existing CUA modelling, both of these were sampling probabilistically. Therefore whilst average results may appear homogenised, the experience of individually modelled people with type 2 diabetes was very different. The economic model outputs were compared to existing CUAs in appendix F 5.3

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					revising the recommendations to take account the limitations of the model as described by the model creators; and the uncertainties and probabilistic outputs of the model. AstraZeneca recommends that the treatment algorithm is fundamentally revised with two key changes: • The inclusion of clear considerations to guide treatment choice according to individual patient characteristics (including weight, risk of hypoglycaemia, age and occupation) at each treatment phase, so that the algorithm clearly supports clinicians to deliver an individualised, "patient-centred care" approach rather than contraindications alone determining drug choice. • Clear incorporation of the positive SGLT2i NICE TA guidance at first intensification (add onto metformin) if there is a significant risk of hypoglycaemia (or its consequences) or a sulfonylurea is contraindicated or not tolerated. <u>References</u> Frier, B. M. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications Nat. Rev. Endocrinol. 10, 711–722 (2014)	

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					doi:10.1038/nrendo.2014.170 Glogner S et al. The association between BMI and hospitalization for heart failure in 83,021 persons with Type 2 diabetes: a population-based study from the Swedish National Diabetes Registry. Diabet Med. 2014 May;31(5):586-94. doi: 10.1111/dme.12340 Inzucchi S.E. et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015 38:1(140-149) Nirantharakumar K et al, Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. Diabet Med 2012; 29: e445–448. O'Hare et al. The new NICE guidelines for type 2 diabetes – a critical analysis. Br J Diabetes Vasc Dis 2015; http://dx.doi.org/10.15277/bjdvd.2015.006 Phung et al. Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes. JAMA. 2010;303 (14):1410-	

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					1418. Public Health England, 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf Williamson DF et al. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000 Oct;23(10):1499-504 Turchin A et al. Hypoglycaemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care 2009; 32: 1153–1157.	
297	Barnsley Hospital NHS Foundation Trust	NICE	General 11 16 17 19	General 22-24 46-47 1-3,10-12,41	I have been a specialist dietitian working specifically in the diabetes area since 2004. The NICE Recommendations for Type 2 Diabetes (2009) and subsequently the NICE Quality Standards for Diabetes (2011) stated, "Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition." (Recommendation 7 in 2008 and Quality Standard 2 in 2011). I believe that this has lead to two events the first being that some people with diabetes are being given conflicting and inappropriate dietary	Thank you for your feedback. Diet is very important in the treatment and management of type 2 diabetes but the section in the guideline on dietary advice was not prioritised for update at the time this guideline was scoped. Therefore it is not possible to make changes to these recommendations as no evidence review has been conducted.

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				10-13	advice by some health professionals (For which I have anecdotal evidence); Secondly that this undermines the role of the specialist dietitian working in the area of diabetes. Dietitians have the specialist knowledge and skills for translating the evidence based dietary recommendations into practical dietary advice for people with diabetes. Further more undergo continuing professional development activities to maintain the knowledge and skills in this area. I would like to propose the recommendation be modified to say "Provide individualised and ongoing nutritional advice from a specialist diabetes dietitian; or healthcare professional with specific expertise and competencies in nutrition." This also raises the question of where other healthcare professions are gaining their expertise and competencies in nutrition. I believe that the provision of dietary advice requires more than just the provision of what people should eat but also the assessment of their dietary intake in order to assess the dietary changes that need to be discussed and agreed with the person who has diabetes. Furthermore whether this "expertise and	

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					competency" is maintained by appropriate CPD activities from an appropriate and qualified source and how would this be vetted? It is important that we as health professionals get the cornerstone of treatment right through assessment, education and the provision of appropriate dietary advice, so that people with diabetes can make an informed choices in the food they eat and be actively involved in their diabetes care. Getting this right can only support further treatment options that are made.	
667	Bayer PLC	NICE	20	General	**Self-monitoring of blood glucose** The draft type 1 diabetes guideline includes two new recommendations regarding the empowerment of people to self-monitor blood glucose (1.6.17 and 1.6.18). We suggest that these recommendations are also important for and applicable to people with type 2 diabetes who are self-monitoring, and therefore suggest that for consistency these recommendations are also included in the type 2 diabetes guideline: *'Educate adults with type 2 diabetes who are self-monitoring their blood glucose about how to interpret their blood glucose level, interpret the results and know what action to take.'* *'Support adults with type 2 diabetes who are self-monitoring their blood glucose to make the best use of data through structured education.'*	Thank you for your feedback. Elements of these recommendations from type 1 diabetes guideline are integrated in the following recommendation in type 2 diabetes: "*If adults with type 2 diabetes are self-monitoring their blood glucose levels, carry out a structured assessment at least annually. The assessment should include:* *• the person's self-monitoring skills* *• the quality and frequency of testing* *• checking that the person knows how to interpret the blood glucose results and what action to take* *• the impact on the person's quality of life* *• the continued benefit to the person* *• the equipment used*."
830	BGP Products	Full	269	9.1	**Inclusion of Pancreatic Exocrine Insufficiency (PEI) in the other management**	Thank you for your feedback. Pancreatic Excorine Insufficiency was not prioritised for

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					section. PEI occurs when the amount of enzymes secreted into the duodenum in response to a meal are insufficient to maintain normal digestive processes. Although there is currently limited data available defining the prevalence of pancreatic exocrine insufficiency (PEI) in patients with diabetes. Available data, based on selected populations, suggest a link between the two. Patients with destructive pancreatic disease (such as chronic pancreatitis and pancreatic cancer) or those undergoing pancreatic surgery, have and increased risk of endocrine and exocrine pancreatic malfunction leading to the development of diabetes and malabsorption respectively. However patients with diabetes have also reported PEI. A literature review by Hardt and Ewald (2011) found from early studies using direct pancreatic function tests (e.g. secretin-pancreozymin) that 52.4% of patients with type 1 and type 2 diabetes had PEI (range 18-100%); with PEI tending to be reported more often in insulin-dependent patients.[xii] More recent studies use the indirect faecal elastase-1 test as an indicator of pancreatic function (<100µg/g = severely	inclusion within this iteration of the guideline.

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reduced; 100-200µg/g = moderately reduced; and >200µg/g = normal), as 60% of patients with concentrations <100µg/g have been shown to suffer from steatorrhoea.[xiii] Studies using indirect function tests show abnormal function in 51% of patients with type 1 (range 26-74%) and 32% of patients with type 2 (28-36%).[xii]

Hardt (2000)[xiv] investigated exocrine pancreatic function in 105 controls and 114 patients with type 1 or type 2 diabetes. Reduced faecal elastase-1 concentrations (<200µg/g) were found in 56.7% of type 1 patients, 35% of type 2 patients and 18% of controls:

<table>
<tr><th>Patients</th><th><100 µg/g
n (%)</th><th>100-200 µg/g
n (%)</th><th>>200 µg/g
n (%)</th></tr>
<tr><td>Controls (n=105)</td><td>5 (4.8)</td><td>14 (13.3)</td><td>86 (81.9)</td></tr>
<tr><td>Type 1 diabetics (n=30)</td><td>9 (30.0)</td><td>8 (26.7)</td><td>13 (43.3)</td></tr>
<tr><td>Type 2 diabetics (n=83)</td><td>14 (16.9)</td><td>15 (18.1)</td><td>54 (65)</td></tr>
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The results were statistically different between controls and type 1 diabetics (P<0.01) and between controls and type 2 diabetics (p<0.05).
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Nunes (2003)[xv] conducted a study to screen patients with diabetes for PEI, (n=42 diabetes, n=38 controls). Diagnosis of PEI was established for a faecal elastase-1 level <200µg/g and <100µg/g. The difference between the two groups was significant for both faecal elastase-1 <200µg/g, and faecal elastase-1 <100µg/g.
<table>
<tr><th>Faecal Elastase -1</th><th>Diabetic</th><th>Control</th><th>P-value OR</th></tr>
<tr><td><100 µg/g</td><td>09 (22%)</td><td>01 (2%)</td><td>P <0.05 OR=11 (1.2 – 84)</td></tr>
<tr><td><200 µg/g</td><td>15 (36%)</td><td>02 (5%)</td><td>P <0.05 OR=10 (2.3 – 47)</td></tr>
</table>
Rathman (2001)[xvi] conducted a study to determine the association between levels of faecal elastase-1 and type 2 diabetes (n=544 diabetic patients, n=544 age and sex matched controls). The results showed that faecal elastase-1 concentrations were lower in type 2 diabetic patients than in non-diabetic controls, suggesting the co-existence of diabetes and impaired pancreatic exocrine function.
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<table>
<tr><th>Faecal Elastase -1</th><th>Diabetic Patients (Type 2)</th><th>Controls</th><th>P–value</th></tr>
<tr><td>< 100 µg/g</td><td>11.9%</td><td>3.7%</td><td>p <0.01</td></tr>
<tr><td>< 200 µg/g</td><td>30.3%</td><td>14.3%</td><td>P <0.01</td></tr>
</table>

A recent audit assessed the presence of gastrointestinal symptoms in patients with diabetes and determined, based on faecal elastase-1 measurement, the presence of possible PEI in those with symptoms. During the audit 19 of 34 symptomatic patients provided a faecal sample for analysis; 7 (37%) of these patients had low levels; 2 severe (<100µg/g) and 5 moderate (100-200µg/g).[xvii]

Vujasinovic (2013)[xviii] investigated the prevalence of PEI in 150 patients with diabetes (50 with type 1; 50 insulin treated with type 2; 50 non-insulin treated with type 2). Faecal elastase-1 was reduced in 8 (5.4%) of patients; mildly reduced (100-200 µg/g) in 4 patients and markedly reduced (<100 µg/g) in 4 patients. The</td><td></td></tr>
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					frequency of PEI was 3 in type 1 diabetes; 5 in insulin treated type 2 and 0 in non-insulin treated type 2. The prevalence in this study is lower than in other studies. The authors speculate that this is mostly due to their strict exclusion criteria, especially excessive alcohol consumption and any other known reason for malabsorption. **Management of PEI** Healthcare professionals managing diabetes in both primary and specialist care settings should be aware of PEI and its clinical manifestations, and should consider cause of gastrointestinal symptoms and steatorrhoea. If PEI is suspected, a faecal elastase-1 test can be used to support diagnosis after excluding other causes Pancreatic enzyme replacement therapy is available and can be initiated with the aim of managing symptoms and improving quality of life.	
242	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	13	Figure 1	Concerning the initial therapy algorithm, there is no mention of the SGLT2 inhibitor class. NICE has requested a multiple technology appraisal (MTA) which includes a review of SGLT2 inhibitor use as first line treatment if metformin is contraindicated or not tolerated. Please consider revising the current lack of reference to SGLT2	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the

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					inhibitors in the initial therapy algorithm or including a statement to outline the initiation by NICE of an MTA for the SGLT2 inhibitor class in this treatment line.	changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
243	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	14 Page 256	Figure 2 20-22	Concerning the first intensification algorithm please consider inclusion of the SGLT2 inhibitor class in the main decision tree rather than in a floating grey box. In the grey box, you state 'that SGLT2i may be appropriate for some patients but is beyond the scope of this guidance'. In addition, you refer to NICE TA288 and TA315. Both of these documents were available prior to June 2014 (your defined cut off for inclusion in the current guideline). Therefore, we would question why the SGLT2 inhibitor class has not been included in the main pathway in the first intensification algorithm. Mindful of the defined cut-off of June 2014, please consider including a footnote stating that empagliflozin has a Single Technology Appraisal (STA) available from NICE in addition to TA288 and TA315 with final guidance due to be issued in March 2015. The current NICE clinical pathway advises clinicians when 'considering dual therapy' to consider prescribing SGLT2 inhibitors (along with sulfonylureas, DPP-4 inhibitors, a thiazolidinedione, and GLP1-Ra). This new guidance seems incongruent to the current NICE pathway guidance and mainstream clinical practice.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
24	Boehringe	Full	15	Figur	In the second intensification, there is again a	Thank you for your comment on how the NICE

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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4	r Ingelheim and Eli Lilly Diabetes Alliance			e 3	floating grey box advising clinicians 'SGLT2-inhibitors maybe appropriate for some patients, but are beyond the scope of this guidance.' Both of these documents were available prior to June 2014 (your defined cut off for inclusion in the current guideline). Therefore, we would question why the SGLT2 inhibitor class has not been included in the main pathway in the second intensification algorithm. Mindful of the defined cut-off of June 2014, please consider including a footnote stating that Empagliflozin has a Single Technology Appraisal (STA) available from NICE in addition to TA288 and TA315 with final guidance due to be issued in March 2015. In the current NICE clinical pathway for considering triple therapy, the guidance advises the use of SGLT2 inhibitors, DPP4 inhibitors, a thiazolidinedione, and GLP-1Ra. This new guidance seems incongruent to the current NICE pathway guidance and mainstream clinical practice. In addition in the summary of clinical advice on 2nd intensification on page 257 there is no mention of the use of SGLT2 inhibitors.	technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
251	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	168	36	The GDG justification for not including placebo controlled trials within the NMA appears overly restrictive. Placebo controlled studies demonstrate the absolute additive effect of add-on therapies and therefore, provide essential and useful information on the effectiveness of the treatments in dual, triple, and add on to	Thank you for your feedback. As explained in section 8.4.1.4 (full guideline), the guideline development group agreed to concentrate on evidence that was of direct relevance to the individual decision problems under consideration. All trials that compared at least 2 treatments in each decision problem were

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					insulin settings. In particular by excluding these studies information on the long-term effectiveness of agents such as DPP-4 inhibitors has been excluded at 52 weeks. Given the GDG's interest in the long-term effectiveness of these agents this data should have been included. The NMAs conducted for the SGLT2 inhibitor appraisals demonstrate that analyses with placebo controlled studies are viable and appropriate.	included, as recommended. Combinations including placebo were not part of the decision problem. A separate question arises as to whether the inclusion of such evidence within the network meta-analyses would have enhanced precision in estimates of effect for the regimens of interest. Such an approach might have allowed more precise estimates to be made, though it is also possible that increased clinical heterogeneity would have introduced unhelpful statistical inconsistency into the models. It should also be noted that other sources of additional indirect evidence beyond the decision set exist – for example, a large amount of evidence comparing regimens that are currently unlicensed in this country, most notably those containing rosiglitazone. The guideline development group and developers took the decision not to extend the network to include any evidence of only indirect value, as coherent networks were generally possible relying on directly relevant trials alone. Data on DPP-4 inhibitors at 52 weeks have been included in the evidence review. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the

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						changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
245	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	260	11 -18	It is stated that long term studies on SGLT2 inhibitors including cardiovascular outcomes are required. It should be noted that 24 month studies are available for all three marketed SGLT2 inhibitors with further 24 month extensions for 2 of these. In addition all have cardiovascular safety studies ongoing with empagliflozin due to report its cardiovascular outcomes study in 2015 (www.clinicaltrials.gov).	Thank you for your feedback. The research recommendation suggests that outcomes should be evaluated for at least 5 years.
249	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Appendix F full economic report	88	Table 65	Repaglinide is suggestive of demonstrating the highest incidence of hypoglycaemia of the agents included in the NMA (metformin, pioglitazone, DPP4 inhibitors and sulphonylureas). Repaglinide should include blood glucose monitoring costs (SMBG) similarly to sulfonylureas. In particular the SmPC for repaglinide recommends additional monitoring.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
246	Boehringer	Full	General	Figures 1,	The GDG comments that due to the fact that differences in lifetime discounted costs for DPP4	Thank you for your feedback. The recommendations have been amended to place

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	Ingelheim and Eli Lilly Diabetes Alliance			2, 3 Table 73 Table 74	inhibitors were mainly in treatment costs, the GDG has recommended the DPP4 inhibitor with the lowest acquisition cost. It is our view that the DPP4 inhibitor which is most appropriate for the patient should be chosen and drug acquisition costs should not form part of the prescribing decision. Differences in licence in dual and triple therapy and dose adjustment in progressive renal disease will influence prescribing choice. These factors have not been incorporated into the health economic analyses.	a greater emphasis on discussing the benefits and risks of each treatment option to include efficacy, safety, the person's clinical circumstances preferences and needs, licenced indications or combinations and costs.
239	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	General	General	The prominence of repaglinide and pioglitazone as initial recommendations in the draft guidelines should be ameliorated and the position of SGLT2 inhibitors and DPP4 inhibitors should be enhanced. The draft guidelines should take a patient centred approach with equal prominence of SGLT2 inhibitors, DPP4 inhibitors, sulphonylureas and TZDs (after metformin) and pursuant to medicines optimisation.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The recommendations are based on the clinical

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						effectiveness review and health economic modelling analysis, and not only the available licensed combinations. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate.
240	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	General	General	When ranking the blood glucose lowering treatment based on their HbA1c lowering effect (3 months, 6 months, 12 months and 24 months), weight reduction (12 and 24 months), dropouts due to AEs, total dropouts, nausea and hypoglycaemia, their ranking positions interchange depending on the outcome measure. The older blood glucose lowering treatments such as repaglinide and pioglitazone tend to rank higher based on efficacy variables such as HbA1c lowering effect (3 months, 6 months, 12 months and 24 months) than the newer class of blood glucose lowering treatments such DPP4 inhibitors and SGLT2 inhibitors. However, the newer class of blood glucose lowering treatments tend to rank higher based on weight reduction (12 and 24 months), dropouts due to AEs, total dropouts, nausea and hypoglycaemia, thus highlighting their individual strengths and weaknesses, and showing that overall (efficacy and safety) there is insufficient data and evidence to strongly demonstrate the superiority of one blood glucose lowering treatment agent over the other. Therefore, the recommendation **after initial drug monotherapy** (metformin) should be a patient	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and

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					centred approach (costs, dosing, adherence, compliance, patient preference, HbA1c lowering effect, side effects, weight reduction, hypoglycaemia and nausea), akin to the ADA/EASD guidelines, to treat to their respective individualised HbA1c targets. Providing the clinician with a choice from the following classes of blood glucose lowering agents: sulphonylureas, thiazolidinedione, DPP-4 inhibitors and SGLT2 inhibitors (the order is not meant to denote any specific preference).	sulfonylurea where metformin is contraindicated or not tolerated. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations.
241	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	General	General	When ranking the blood glucose lowering treatment based on their HbA1c lowering effect (3 months, 6 months, 12 months and 24 months), weight reduction (12 and 24 months), dropouts due to AEs, total dropouts, nausea and hypoglycaemia, their ranking positions interchange depending on the outcome measure. The older blood glucose lowering treatments such repaglinide and pioglitazone tend to rank higher based on efficacy variables such as HbA1c lowering effect (3 months, 6 months, 12 months and 24 months) and some safety variables compared to the newer oral class of blood glucose lowering treatments such DPP4 inhibitors and SGLT2 inhibitors. However, the newer class of oral glucose lowering treatments tend to rank higher based on some selected safety variables, highlighting their individual strengths and weaknesses, and showing that overall (efficacy and safety) there	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. The

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					is insufficient data and evidence to strongly demonstrate the superiority of one blood glucose lowering treatment over the other. Therefore, the recommendation **for first intensification** should be a patient centred approach (costs, dosing, adherence, compliance, patient preference, HbA1c lowering effect, side effects, weight reduction, hypoglycaemia and nausea), akin to the ADA/EASD guidelines, to treat to their respective individualised HbA1c targets. Providing the clinician with a choice from the following classes of blood glucose lowering agents: sulphonylureas, thiazolidinedione, DPP-4 inhibitors and SGLT2 inhibitors, for first intensification (the order is not meant to denote any specific preference).	recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
247	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	General	General Table 61 Table 73	The recommendation of repaglinide at initial therapy if metformin intolerant, or dual therapy in addition to metformin takes no consideration of the restricted licence of repaglinide in dual therapy (repaglinide SmPC). This is echoed in commentary by the GDG (table 61). In addition the use of pioglitazone, sulphonylureas and DPP4 inhibitors, which are not licensed in combination with meglitinides, is not accounted for from a practical perspective but echoed in the commentary by the GDG (table 61). The health economic analysis for first intensification included 7 treatments that could be modelled, all of which contained	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In

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					metformin and none of which contained repaglinide (table 73). Patients will therefore need to be switched from repaglinide to alternate treatments once second or third line therapy is required and therefore the utility of repaglinide in clinical practice is questioned due to the complex nature of the recommendation created as part of the guidelines.	addition, recommendations referring to repaglinide make clear in retained footnotes that "Repaglinide has a marketing authorisation for use only as monotherapy or in combination with metformin. Therefore, for people who cannot take metformin, there is no licensed combination containing repaglinide that can be offered at first intensification. Patients should be made aware of this when initial therapy is being discussed" and to "Be aware that initial drug treatment with repaglinide should be stopped and the drugs in the dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug." This information is also reflected in the algorithm.
248	Boehringer Ingelheim and Eli Lilly Diabetes Alliance	Full	General	General Table 61	The GDG acknowledges the three times daily regimen of repaglinide but concludes it unlikely to have an impact on disutility since metformin is taken three times daily (table 61). In fact metformin may be taken twice daily or three times daily and therefore the impact on disutility may be possible. In addition the impact of adherence has not been considered as part of the cost effectiveness analysis. Evidence points towards the fact that the adherence is enhanced with once daily regimens compared with multiple tablets taken per day (Donnan et al, 2002).	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
250	Boehringer	Full	General	General	The GDG has highlighted the limitations of the thiazolidinedione class and pioglitazone	Thank you for your feedback. The guideline development group has reflected on the clinical

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	Ingelheim and Eli Lilly Diabetes Alliance			Table 73 Table 74	specifically. Pioglitazone is not recommended in patients with a history of bladder cancer and heart failure. In addition it is not recommended in those at risk of osteoporosis. Its use is therefore highly restricted in the elderly and female populations. In addition rosiglitazone has been removed from the UK market and therefore the thiazolidinedione class has severely restricted usage in clinical practice.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
366	British Medical Association	NICE	12	General	There may be major unforeseen consequences in the wide use of Repaglinide - an agent that is very little used, particularly in the UK, and which has very little follow-on data. Other oral or parenteral treatments might be more appropriate.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
363	British Medical	NICE	46	General	Most of the advice is reasonable though the emphasis on structured education programmes -	Thank you for your feedback.

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	Association				with yearly review - does depend on local resources and sufficient staff to achieve this. The GPC Clinical & Prescribing subcommittee discussed local variations and one GP member commented that "in our area, although we have an X-Pert Patient Programme running it tends to be reserved for those whose control needs improvement, not the whole diabetic population which would require more investment."	
368	British Medical Association	NICE	50	General	Although dietary advice is integral and the document is weighted towards that, smoking cessation and lipid control are only briefly mentioned in the document, and deserve prominence.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence on smoking cessation or on lipid control in people with type 2 diabetes. There is a comprehensive set of NICE guidance on smoking cessation which will feed into the NICE pathway for the type 2 diabetes guideline. There is also recently published guidance on lipid modification (CG181) which is cross referred to in the guideline update which includes recommendations on the management of lipids in people with type 2 diabetes. The NICE pathways online tool is the main interface through which clinicians now access NICE guidance and will enable easy navigation between type 2 diabetes and all pieces of related NICE guidance.
364	British Medical Association	NICE	General	General	The need for tight glucose control should be less vigorous in the elderly. Both ADVANCE-ON and UKPDS both emphasise that blood pressure and possibly lipid control is more	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included

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					important in this age group than tight glucose control, which may cause harms.	recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
365	British Medical Association	NICE	General	General	NICE should give higher HbA1c targets for this age group, those with 10 years or less reasonable life expectancy, which would give the opportunity to emphasise tight control in younger patients. The Joint Position Statement from ADA/EASD (American Diabetes Association/European Association for the Study of Diabetes) make the point that results from large trials have also suggested that overly aggressive control in older patients with more advanced disease may not have significant benefits and may indeed present some risk.	Thank you for feedback. Recommendation 1.6.9 provides guidance on relaxing HbA1c targets in different circumstances including in people unlikely to achieve longer-term risk-reduction benefits such as those with a reduced life expectancy.
367	British Medical Association	NICE	General	General	The guideline does refer to Lantus but for the insulin-sensitive patient it could be a first-line therapy, rather than isophane insulin to avoid the risk of nocturnal hypos.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased

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						emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Therefore, healthcare professionals have the flexibility to prescribe insulin detemir or insulin glargine for people whose lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes.
369	British Medical Association	NICE	General	General	The guideline emphasises tight control for the young but the option of higher HbA1c targets for the elderly or those with limited life expectancy should be clearer. Patients will have differing views as to the benefits and problems of tight glucose control and emphasis should be on education and then respecting patients' choices.	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
84	British Society of Interventional Radiology (BSIR)	NICE	General	General	There are no specific comments on behalf of BSIR.	Thank you for your feedback.
526	Cardiff University/ Pharmatelligence	Full	General	General	The guidelines document looks naïve to experienced diabetes researchers.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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						recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
527	Cardiff University/ Pharmatelligence	Full	General	General	It should be clearly stated at the outset whether the purpose of the proposed guidelines is to achieve maximum clinical benefit from existing drugs that have been reviewed, or to achieve cost minimisation. Clearly the latter was at the forefront of the committees thinking.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
528	Cardiff University/ Pharmatelligence	Full	General	General	In general, the proposed guidelines appear to be quite good to achieve the objective of cost minimisation but the justification is more by accident that rationale thinking and evidence.	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines.
52	Cardiff	Full	Gene	Gen	The issue of the use of ripaglinide is almost	Thank you for your feedback. The guideline

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

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9	University/ Pharmatelligence		ral	eral	weird, and stands out as being odd. Having said that, I completely agree that we should try and prevent the use of SUs as much as possible.	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
530	Cardiff University/ Pharmatelligence	Full	General	General	The omission of the DPP4s is apparent. I think that you should include a stamen that all DPP4s should be considered if the manufacturers match the price of alogliptin.	Thank you for your feedback. DPP-4s have been included at initial therapy, first and second intensification. It is not the role of NICE guidelines to suggest price matching/thresholds for particular therapies.
531	Cardiff University/ Pharmatelligence	Full	General	General	Omission of clear guidance on the use of the GLP-1s needs to be thought through otherwise they will be used willy-nilly.	Thank you for your feedback. Based on the updated evidence review and health economic analysis, the guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care

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						professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
532	Cardiff University/ Pharmatelligence	Full	General	General	Clear guidance on who should and who should not receive pioglitazone should be included. Pioglitazone is the most sensible second line combination therapy taken with metformin, but there are people who should avoid it.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are

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						appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
533	Cardiff University/ Pharmatelligence	Full	General	General	Yu should consider including a price threshold for the DPP4s where they would be used in preference to pioglitazone. This would be unusual but appropriate.	Thank you for your feedback. It is not the role of NICE guidelines to suggest price thresholds for particular therapies.
534	Cardiff University/ Pharmatelligence	Full	General	General	There is serious conjecture about the use of insulin in type 2 diabetes and the guidelines do not mention any of this debate.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
535	Cardiff University/ Pharmatelligence	Full	General	General	There should be a discussion about why NICE is deviating from the EASD/ADA guidelines.	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to

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						provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines.
891	Cheshire Diabetes Network	NICE Full	General	General	**Screening** 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.	Thank you for your feedback. This topic is not within the scope at this guideline that focuses on management.

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					Urinalysis is not a recommended screening tool.	
892	Cheshire Diabetes Network	NICE Full	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 (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.	Thank you for your feedback. This topic is not within the scope at this guideline that focuses on management.

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					• 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.	
893	Cheshire Diabetes Network	NICE Full	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. • **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,	Thank you for your feedback. As stated in the background (see section 2.1 in the full guideline), an HbA1c threshold of 48 mmol/mol (6.5%) indicates the presence of diabetes mellitus.

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					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 **Interpretation of OGTT (WHO, 2000):** As before	
894	Cheshire Diabetes Network	NICE General	General	General	We found that whilst the document has considered many aspects of Diabetic assessment and Type 2 diagnoses, regarding development and the Categorisation and overall implementation, the omission of a Practice Nurse from the guideline panel, who are most likely to be categorising patient initially, could have added to the Guideline development and to the overall Richness of this guidance.	Thank you for your feedback. A practice nurse was part of the guideline development group and contributed to the discussions and decision-making of the guideline committee.
388	Clinical Advisory Group for Diabetes	Full	13 14 ,15	General	**Algorithm** Need to add rescue treatment with insulin in the algorithm across the sides	Thank you for your feedback. This information has been added to the algorithm.
379	Clinical Advisory Group for Diabetes	NICE	14	1.2.2	**Education** Given that only about ten per cent of newly diagnosed people with diabetes access the existing programmes, should we also consider different means of education e.g. peer support, locally developed education programmes, online	Thank you for your comment. Education was not prioritised within the guideline for update. This decision was taken following a workshop conducted with stakeholders during the scoping of the guideline and stakeholder consultation. It may be possible to address this area in a future

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					programmes etc?	iteration of the guideline.
380	Clinical Advisory Group for Diabetes	NICE	18	1.5.1	**Antiplatelet therapy** Special circumstances will need to be added to ensure that those with high risk of cardiovascular disease are give aspirin eg. microalbuminuria	Thank you for your feedback. While the guideline development group recognised that microalbuminuria may be an indicator of cardiovascular risk as it may be an early signal of decline in kidney function, it is also manifested in people with type 2 diabetes and normal renal function. There are other ways of assessing cardiovascular risk such as hypertension and in the absence of evidence on the effects of antiplatelet therapy in this specific subgroup, the Group did not consider it appropriate to make a recommendation for people with type 2 diabetes and microalbuminuria. The Linking Evidence to Recommendations table (see section 7.2 in the full guideline) has highlighted that it would be beneficial for large ongoing trials to consider the effects of antiplatelet therapy within this specific subgroup.
381	Clinical Advisory Group for Diabetes	NICE	19	1.6.8	**Blood glucose targets** We welcome the blood glucose targets, in particular the *intensification* target of 53 (7%) for those whose Hba1c gets to 58mmol/mol. This is both sensible and practical.	Thank you for your feedback that the recommended blood glucose targets are sensible and practical.
382	Clinical Advisory Group for Diabetes	NICE	21	1.6.13	Blood glucose self-monitoring This may be too restrictive particularly with regards to 'symptomatic' hypoglycaemia. This downplays the importance of testing in people on medications such as sulphonylurea who may experience asymptomatic hypoglycaemia or would benefit from testing to understand the	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose (SMBG) should

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					effect of food and exercise on their blood glucose levels. Should 'symptomatic' should be removed so that testing can be considered for anyone who experiences a hypo? Testing should also be considered for anyone who is on any medication that is accompanied with risks of hypoglycaemia irrespective of whether they drive or operate machinery. Self-monitoring should also be considered for people with poor control or those who may require the added motivation of monitoring the effect of lifestyle changes on blood glucose levels.	not be recommended. The recommendation has been amended to include the following phrase "there is evidence of hypoglycaemic episodes". There was no evidence to indicate that SMBG as a motivation tool was clinically or cost effective and therefore has not been included in the recommendation.
383	Clinical Advisory Group for Diabetes	NICE	22	1.6.19 1.6.20	**Initial treatment - repaglinide** We understand the rationale for metformin, and also the use of repaglinide as first choice for those intolerant of metformin as repaglinide may be used in renal failure, and like metformin it is 3 times a day. It is a better as first choice compared to sulfonylureas. However implementation may be problematic as: • repaglinide is not currently in common use. • It is not licensed for use in the over 75s • combination treatment – repaglinide is only licensed for use metformin, hence at first intensification of treatment, two new drugs will need to be added	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise

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					Initial treatment – pioglitazone We do not agree with pioglitazone as first option at this point because of weight implications (although we appreciate that pioglitazone is useful re insulin sensitivity) Our suggestions are: • No change re repaglinde • Add metformin SR for those with abdominal side effects • Because of weight gain and risks of osteoporosis, heart failure with pioglitazone, make DPP-4 inhibitor the option here.	particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
384	Clinical Advisory Group for Diabetes	NICE	22	1.6.21	Acquisition cost We welcome the suggestion to use the medicine with lowest acquisition cost	Thank you for your feedback.
385	Clinical Advisory Group for Diabetes	NICE	23	1.6.22	**First intensification** As above re pioglitazone and adverse effects – we would welcome the analysis being re-evaluated with greater weighting given to weight gain as a negative aspect. This would enable more emphasis to be placed on the 'weight-friendly' treatments e.g. DPP-4 inhibitors and SGLT2 inhibitors	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking

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						Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
387	Clinical Advisory Group for Diabetes	NICE	23 24 25	1.6.22 1.6.27 1.6.29	**Second intensification** The use of GLP1 may need to be reviewed, and the BMI criteria is disappointing We suggest Consider GLP1 (at first intensification if BMI >35 Consider GLP1 (at second and third intensification for BMI>30)	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
386	Clinical Advisory Group for Diabetes	NICE	27	1.6.34	**Non-analogue insulin use** We welcome the use of non-analogue insulins given the cost issues, although clear guidance on when the analogues come off patent is needed – this need to be kept under review	Thank you for your feedback.
376	Counterweight Ltd.	Full	15	1.3.5	Prevalence of BMI >35kg/m^2 is 6% women and 11% in men of which 11% and 20% respectively have diagnosed Type 2 diabetes. ***Health Survey England 2010.***	Thank you for your feedback.
377	Counterweight Ltd.	Full	15	1.3.5	Recommendation from **Scottish Intercollegiate Guidelines Network (SIGN) 115**: in patients with BMI>35 kg/m2 obesity-related comorbidities are likely to be present therefore weight loss interventions should be targeted to improving these comorbidities; in many individuals a greater than 15-20% weight loss	Thank you for your feedback. It was not within the scope of the guideline to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has guided the structure of the guideline. NICE also

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					(will always be over 10 kg) will be required to obtain a sustained improvement in comorbidity.	has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.
378	Counterweight Ltd.	Full	15	1.3.5	For adults with Type 2 diabetes and BMI >30kg/m^2, weight loss of ≥ 15kg is required for the normalisation of glucose and insulin, there is clear evidence this can be achieved by a combined medical programme of diet, exercise and anti-obesity drugs can generate and maintain >15kg weight loss for many patients. ***Rejeski WJ, Ip EH, Bertoni AG, Bray GA, Evans G, Gregg EW, Zhang Q. Lifestyle change and mobility in obese adults with type 2 diabetes. NEJM 2012; 366(13):1209-1217***	Thank you for your feedback. It was not within the scope of the guideline to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.
538	Covidien	NICE	22	20 (#60)	We would like to reiterate the previous comment with regards to the NICE version of the Clinical Guideline and as outlined above draw NICE' attention to the wealth of evidence supporting this therapy and proving that bariatric/metabolic surgery should be considered as a beneficial treatment option for a specific patient cohort within NICE recommendation. Again, we urge NICE to consider these new findings on the clinical effectiveness of bariatric/metabolic surgery in a type 2 diabetes	Thank you for your feedback. It was not within the scope at this guideline update to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to

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					patient subgroup (Schauer et al., 2014) and the increasing experience of bariatric/metabolic surgery in clinical practice in type 2 diabetes into account within the context of the Clinical Guideline, and include this treatment option as a consideration in the recommendations for blood glucose management of these patients. Specifically, we propose that an addition is made to the 'Recommendations' section: Recommendation #60 (p.22). Under this recommendation we propose that the following statement should be included: • *Consider bariatric/metabolic surgery for:* - patients with difficult-to-control diabetes and a BMI equal to or greater than 30 kg/m^2	assist in weight loss.
539	Covidien	NICE	22	37 (#61)	Specifically, we propose that an addition is made to the 'Recommendations' section: Recommendation #61 (p.22). Under this recommendation we propose that the following statement should be included: • *Consider bariatric/metabolic surgery for:* - Patients with a BMI of 35 or over	Thank you for your feedback. It was not within the scope at this guideline update to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet,

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					who have recent-onset type 2 diabetes *or* - for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations With type 2 diabetes who have not had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1%] in HbA1c or weight loss of at least 3% of initial body weight in 6 months). Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Ali Aminian, M.D., Claire E. Pothier, M.P.H., Esther S.H. Kim, M.D., M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D. for the STAMPEDE Investigators N Engl J Med 2014; 370:2002-201	physical activity and behaviourial interventions to assist in weight loss.
536	Covidien	Full and NICE versions	General	General	Thank you for the opportunity to comment on this guideline update. We are concerned, however, that there is no mention in either the full guideline or current NICE guideline of the role of bariatric surgery in the management of type 2 diabetes, and we would like to draw the attention of NICE to a recent randomised controlled trial (RCT) comparing medical therapy alone vs surgical interventions in patients with uncontrolled type 2 diabetes.	Thank you for your feedback. It was not within the scope at this guideline update to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes

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					There are also now more than a dozen published randomized clinical trials directly comparing surgical interventions against a variety of medical and lifestyle approaches to weight loss and metabolic disease. All of these studies found that when surgery is added to medical care, superior outcomes are achieved compared to conventional or even intensive non-surgical treatments alone, in terms of glycaemic and metabolic control, diabetes remission, weight loss, medication usage, and quality of life. These recently published data would not have been included in the evidence review, therefore to ensure that the Clinical Guideline is contemporary on publication we recommend that NICE considers these study findings as described in our subsequent comments.	recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.
537	Covidien	Full	General	General	In a three-group, randomized, controlled, single-center study involving 150 obese patients, the effects of intensive medical therapy were compared with those of gastric bypass or sleeve gastrectomy Schauer et al. reported that at 3 years, each of the two surgical procedures was superior and the use of glucose-lowering medications including insulin was reduced from baseline in the two surgical groups to intensive medical	Thank you for your feedback. It was not within the scope at this guideline update to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes

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					therapy alone. Exploratory targets were reached for glycated hemoglobin of 6.5% and 7.0%, with or without the use of diabetes medications (P<0.05 for all comparisons) with the target glycated hemoglobin level of 6.0% or less being achieved in 5% of the patients in the medical-therapy group, as compared with 38% of those in the gastric-bypass group (P<0.001) and 24% of those in the sleeve-gastrectomy group (P=0.01). Schauer et al. also reported a greater reduction in the BMI in the two surgical groups, meeting the criterion for the primary end point predicted both by a reduction in the BMI (odds ratio, 1.33; 95% CI, 1.15 to 1.56; P<0.001) and by a duration of diabetes of less than 8 years (odds ratio, 3.3; 95% CI, 1.2 to 9.1; P=0.02). The authors suggest several mechanisms to explain superior and sustained glycaemic control and weight reduction concluding that bariatric surgery represents a potentially useful strategy for the management of type 2 diabetes, allowing many patients to reach and maintain therapeutic targets of glycaemic control that otherwise would not be achievable with intensive medical therapy alone with some patients even having complete diabetes remission and all experiencing improved quality of life. Given this highly consistent Level-1 evidence, a role for bariatric/metabolic surgery in the	recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.

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					treatment of T2DM is now supported by most major diabetes organizations, including the American Diabetes Association (ADA) and the International Diabetes Federation (IDF), we would urge NICE to take these new and important findings into consideration and issue this guidance in line with recently issued NICE Clinical guideline (CG189, 2014) which also suggests that bariatric/metabolic surgery could be considered in patients with difficult-to-control diabetes and a BMI equal to or greater than 30 kg/m^2. Under this recommendation we propose that the following statement should be included: • *Consider bariatric/metabolic surgery for:* - Patients with a BMI of 35 or over who have recent-onset type 2 diabetes *or* - patients with difficult-to-control diabetes and a BMI equal to or greater than 30 kg/m^2 *or* - for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations	

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					Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. Ann Surg. 2014 Oct;260(4):617-22	
540	Covidien	Full And NICE	General	General	A substantial body of evidence has accumulated, including numerous randomized clinical trials, demonstrating that bariatric/metabolic surgery can achieve excellent control of hyperglycemia and often promote diabetes remission, reducing cardio-metabolic risk and mortality. Research on the mechanisms of action of these procedures has also revealed a critical role of the gastrointestinal tract in glucose homeostasis. Such evidence provides a biological and clinical rationale for gastrointestinal surgery to be considered in the treatment of type 2 diabetes (T2DM). Many studies have shown that bariatric/metabolic surgery in patients with diabetes is also safe and cost-effective. There are now more than a dozen published randomized clinical trials directly comparing surgical interventions against a variety of medical and lifestyle approaches to weight loss and metabolic disease. All of these studies found that when surgery is added to medical care, superior outcomes are achieved compared	Thank you for your feedback. It was not within the scope at this guideline update to consider weight-loss interventions. However, the guideline development group was keen to emphasise the importance of diet, physical activity in lifestyle within the type 2 diabetes guideline, which which has influenced the structure of the guideline. NICE also has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.

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					to conventional or even intensive non-surgical treatments alone, in terms of glycemic and metabolic control, diabetes remission, weight loss, medication usage, and quality of life. Among more than 1,000 patients enrolled in these randomized trials, there have been no surgery-related deaths to date. Given this highly consistent Level-1 evidence, a role for bariatric/metabolic surgery in the treatment of T2DM is now supported by most major diabetes organizations, including the American Diabetes Association (ADA) and the International Diabetes Federation (IDF). In fact, recently issued NICE guidelines also suggested that bariatric/metabolic surgery could be considered in patients with difficult-to-control diabetes and a BMI equal to or greater than 30 kg/m^2. We would therefore request that the proposed NICE diabetes guidelines consider surgery as an option for patients with difficult-to-control diabetes and obesity, as this would be consistent with available medical evidence and current NICE guidelines for bariatric/metabolic surgery. In September 2015, London and the UK will host the 3rd World Congress on Interventional Therapies for Type 2 Diabetes jointly with the 2nd Diabetes Surgery Summit (DSS-II). The DSS-II is a consensus conference organized in partnership with leading world diabetes	

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					organizations – including Diabetes UK, the ADA, the EASD, and many others – to more specifically define the roles for surgery in diabetes treatment algorithms. The World Congress/DSS is expected to produce a document that will serve as a global reference for the use of bariatric/metabolic surgery as a diabetes intervention (i.e., as "diabetes surgery"). We hope it may be possible for NICE to consider amending their current diabetes treatment guidelines to acknowledge a role for bariatric/metabolic surgery in selected cases. Alternatively, we wonder if it might be possible to postpone the release of the new guidelines until after the World Congress/DSS in London (September 28-30, 2015 www.wcitt2d.org). To this end, we would like to extend an official invitation for NICE representatives to attend the event as guest experts, so they can consider evidence presented at the conference before finalising the new diabetes document. This may allow for appropriate amendment to the proposed guidelines that recognizes this important new aspect of diabetes treatment. References 1. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. The New England journal of	

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					adjustable gastric banding in severely obese adolescents: A randomized trial. JAMA - Journal of the American Medical Association 2010;303(6):519-26. 7. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, et al. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: A randomized controlled trial. JAMA - Journal of the American Medical Association 2012;308(11):1142-49. 8. O'Brien PE, Dixon JB, Laurie C, Skinner S, Proietto J, McNeil J, et al. Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program: A randomized trial. Annals of Internal Medicine 2006;144(9):625-33. 9. Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X. Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: A randomized controlled trial. Diabetes Research and Clinical Practice 2013. 10. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: A randomized controlled trial. Obstetrical and Gynecological Survey 2008;63(6):372-73. 11. Heindorff H, Hougaard K, Larsen PN. Laparoscopic adjustable gastric band increases weight loss compared to dietary treatment: A	

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					randomized study. Obesity surgery 1997;7(4):300-01. 12. Courcoulas AP, Goodpaster BH, Eagleton JK, Belle SH, Kalarchian MA, Lang W, Toledo FG, Jakicic JM. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg. 2014 Jul;149(7):707-15. 13. Halperin F, Ding SA, Simonson DC, Panosian J, Goebel-Fabbri A, Wewalka M, Hamdy O, Abrahamson M, Clancy K, Foster K, Lautz D, Vernon A, Goldfine AB. Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg. 2014 Jul;149(7):716-26. 14. Wentworth JM, Playfair J, Laurie C, Ritchie ME, Brown WA, Burton P, Shaw JE, O'Brien PE. Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. Lancet Diabetes Endocrinol. 2014 Jul;2(7):545-52. 15. Parikh M, Chung M, Sheth S, McMacken M, Zahra T, Saunders JK, Ude-Welcome A, Dunn V, Ogedegbe G, Schmidt AM, Pachter HL. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker	

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					of success. Ann Surg. 2014 Oct;260(4):617-22	
469	Department of Health	NICE	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Thank you for your feedback.
514	Diabetes Reference Group Conwy and Denbighshire	Full	13	1.1.1	Explain how the medicines to be stopped would be beneficial to the patient's health and the measures that can be used to demonstrate this.	Thank you for your feedback. This asessment would be undertaken on an individual basis and, after balancing both benefits and risks, medications discontinued if thought not to be contributing to the patient's overall health and wellbeing.
517	Diabetes Reference Group Conwy and Denbighshire	NICE	13	1.2.1	Strongly agree on need for education	Thank you for your feedback.
515	Diabetes Reference Group Conwy and Denbighshire	Full	13	1.2.1	Annual reinforcement and review of diabetes education to be part of the personalised diabetes management plan. Such plans do not exist in many surgeries and not in my own. Who should enforce this?	Thank you for your comment. This suggestion will be passed on to the NICE guidance implementation team.
518	Diabetes Reference Group Conwy and Denbighsh	NICE	14	1.2.2	Absolutely Vital	Thank you for your feedback.

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513	Diabetes Reference Group Conwy and Denbighshire	Full	14	1.2.2	Training to be delivered by "suitably qualified and competent people" not "trained deliverers" i.e. anyone of diabetes education. Attendees of structured education need to be able to discuss their needs and requirements with specialists in the field of diabetes at such events.	Thank you for your comment. The education section within the type 2 diabetes guideline was not prioritised for update; therefore it is not possible to make changes to these recommendations without an evidence review. However, the type 1 diabetes guideline did look at evidence on structured education as part of their update and the type 2 diabetes guideline has been checked for consistency across both guidelines.
519	Diabetes Reference Group Conwy and Denbighshire	NICE	15	General	Dietary advise and education is vital needs to be available locally	Thank you for your feedback.
520	Diabetes Reference Group Conwy and Denbighshire	NICE	16	1.3.9	Better Knowledge of Diabetes needed and food suitable for diabetics monitored.	Thank you for your feedback.
516	Diabetes Reference Group Conwy and Denbighsh	Full	17	1.4.11	Not every diabetic can tolerate Thiazide medicines so care should be taken when considering this treatment.	Thank you for your feedback. It is not within the scope at this guideline update to alter the recommendations on blood pressure therapy. The recommendations provide a guide for treatment for a majority of patients but the guideline does advise that treatment and

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	ire					management should be individualised and that recommendations should not replace individual clinical judgement.
521	Diabetes Reference Group Conwy and Denbighshire	NICE	20	1.6.9	Agree	Thank you for your feedback.
522	Diabetes Reference Group Conwy and Denbighshire	NICE	21	General	Agree	Thank you for your feedback.
554	Diabetes UK	NICE	13	1.1.1	**Individualised care** The recommendation to individualise care is very welcome. We should also emphasise the fact that some patients may have had Type 2 diabetes for a while before diagnosis and with possible complications (e.g. retinopathy). Therefore initiating therapy has to be tailored in order not to worsen such complications. Additionally, it is important to ensure that systematic processes are used to tailor treatments. Therefore, care and support planning, as recommended in the NICE quality standards 6, should be included within the	Thank you for your feedback. The guideline emphasises that care should be tailored to individual needs and that co-morbidities should be considered (which will include complications). Annual review is highlighted at several points in the document, including structured education with annual reinforcement and review.

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					guidelines and emphasised as recommended good practice.	
555	Diabetes UK	NICE	13	1.2.1	**Patient education** We understand and support the need for structured education programmes to be the gold standard. However, given that only about ten per cent of newly diagnosed people with diabetes access such programmes, we should consider different means of education e.g. peer support, locally developed education programmes, online programmes etc. **Even though this recommendation was not reviewed for this consultation, we see patient education as an integral part of diabetes management. Given the low levels of availability, and uptake, of current structured education programmes in certain areas of the country, we think it is extremely important to consider other options in addition to, not replacements of, structured education, and to encourage uptake.**	Thank you for your comment. This suggestion will be passed on to the NICE guidance implementation team.
556	Diabetes UK	NICE	16	1.4.3	**Blood pressure targets** Agree with upper limits. However there should be guidance on lower levels, given the evidence that there is no benefit (indeed possible harm) of pursing targets that are too low. **Even though this recommendation was not reviewed for this consultation, we feel that the dangers of very low blood pressure**	Thank you for your comment. This section of the type 2 diabetes guideline was not prioritised for update and the recommendations have been brought forward from the previous iteration of the guideline unchanged. As no further evidence reviews have been conducted, it is not possible to make any changes to these recommendations.

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					should be highlighted	However, the suggestion has been logged and will be taken into account when the guideline is next considered for update.
557	Diabetes UK	NICE	18	1.5.1	**Antiplatelet therapy in primary CVD prevention** This ignores the extremely high risk of Cardiovascular disease in people with microalbuminuria (eGFR <60 ml/min). It also does not consider the data from the STENO 2 study that showed in people with Type 2 diabetes and microalbuminuria, aspirin 75 mg daily as part of a package of intensive care substantially reduces the incidence of CVD, progression of renal disease and need for laser therapy. We would suggest modifying this recommendation to: Do not use antiplatelet therapy generally in individuals without CVD. However, consider its use in those with any evidence of chronic kidney disease (albuminuria or eGFR <60 ml/min).	Thank you for your feedback. While the guideline development group recognised that microalbuminuria may be an indicator of cardiovascular risk as it may be an early signal of decline in kidney function, it is also manifested in people with type 2 diabetes and normal renal function. There are other ways of assessing cardiovascular risk such as hypertension. The STENO-2 trial compared a multifactorial intervention that included components all of which could influence cardiovascular outcomes (use of aspirin (75 mg), renin–angiotensin system blockers and lipid-lowering agents and tight glucose regulation) with conventional therapy. Therefore, the group considered that the findings could not robustly be extrapolated to reflect the true effects of aspirin alone. Therefore, it was not considered appropriate to make a recommendation for this specific subgroup. The Linking Evidence to Recommendations table (see section 7.2 in the full guideline) has highlighted that it would be beneficial for large ongoing trials to consider the effects of antiplatelet therapy within this specific subgroup.
558	Diabetes UK	NICE	18	1.6	**Blood glucose target** The guidelines do not provide guidance on target blood glucose levels for people who self-	Thank you for your feedback. No evidence was identified in optimal pre and post prandial blood glucose targets. Therefore, the guideline

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					monitor. As people are encouraged to self-monitor, there should be set target levels to aim for. Without any guidance on what levels of blood glucose to aim for pre and post prandial, it would be difficult for clinicians to have a meaningful conversation with their patients who self-monitor. Perhaps, consider targets similar to the ones in the Type 1 diabetes guidelines.	development group was not confident in making such recommendations in the absence of evidence.
559	Diabetes UK	NICE	19	1.6.8	**HbA1c target** This recommendation suggest waiting until levels go beyond 58mmol/mol (7.5%) before intensifying treatment. Is 58mmol/mol (7.5) not too high? Should we be looking at above 53mmol/mol (7%)? We are concerned that intensification is being left too long. We propose that following any change of medication, HbA1c should be further assessed within three month, and if target HbA1c are not met further intensification of treatment should be considered.	Thank you for your feedback. The guideline development group purposely did not select a drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) as it was considered too low and inappropriate for most people as the condition progresses. In addition, the group considered the natural fluctuating error observed in HbA1c measurements of about 2 mmol/mol (0.2%). Recommendation 1.6.1 provides guidance on measuring HbA1c levels at 3-6 monthly intervals depending on individual needs until HbA1c is stable on unchanging therapy.
560	Diabetes UK	NICE	21	1.6.13	**Blood glucose self-monitoring** The list of scenarios to consider blood glucose self-monitoring is too restrictive particularly with regards to 'symptomatic' hypoglycaemia. This downplays the importance of testing in people on medications such as sulphonylurea who may experience asymptomatic hypoglycaemia or would benefit from testing to understand the effect of food and exercise on their blood glucose levels. We believe 'symptomatic'	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose (SMBG) should not be recommended. The recommendation has been amended to include the following phrase "there is evidence of hypoglycaemic episodes".

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					should be removed so that testing can be considered for anyone who experiences a hypo. Testing should also be considered for anyone who is on any medication that is accompanied with risks of hypoglycaemia irrespective of whether they drive or operate a machinery. Self-monitoring should also be considered for people who may require the added motivation of monitoring the effect of lifestyle changes on blood glucose levels. **Diabetes UK survey shows what people use blood glucose monitoring for.** **http://www.diabetes.org.uk/Documents/Reports/access-test-strips-report-0813.pdf**	There was no evidence to indicate that SMBG as a motivation tool was clinically or cost effective and therefore has not been included in the recommendation.
561	Diabetes UK	NICE	21	1.6.13	**Blood glucose self-monitoring** There is a recommendation for short-term monitoring for people who start steroid treatments. Short-term monitoring should also be considered for those with intercurrent illness or any condition (or circumstances) likely to destabilise blood glucose control. Short-term self-monitoring should also be considered for people who may require the added motivation of knowing the effect of lifestyle changes on blood glucose levels.	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose (SMBG) should not be recommended. There was no evidence to indicate that SMBG as a motivation tool was clinically or cost effective and therefore has not been included in the recommendation.
562	Diabetes UK	NICE	22	1.6.18	**Metformin** In addition to the usual cautions about kidney disease, it would be very useful to add the	Thank you for your feedback. Recommendation 1.6.20 (NICE version) suggests to "*Gradually increase the dose of standard-release metformin*

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					recommendation that any individual prescribed metformin is cautioned to stop it temporarily if they become acutely unwell, particularly with vomiting or diarrhoea**.**	*over several weeks to minimise the risk of gastrointestinal side effects in adults with type 2 diabetes.*"
563	Diabetes UK	NICE	22	1.6.19	**Initial drug treatment** • The fact that repaglinide is mostly taken three times a day, raises serious concerns about adherence issues. Other therapies with less dosing would be preferable. • There is the added complication that repaglinide is not licensed with other oral glucose lowering agents apart from metformin, so that when a second agent is needed, a further change which requires an additional time and effort to explain the situation to the person with diabetes. In practice, this will be making life much more difficult for the person with Type 2 diabetes. • Safety concerns exist regarding Pioglitazone; potential risks including bone fractures, weight gain, bladder cancer etc. These should be highlighted and other alternatives should be considered first. • There is a useful guidance on when Metformin could be contraindicated (in	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2

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					recommendation 1.6.18). There should be a similar statement of when Pioglitazone could be contraindicated. For example those who have a heart failure, or at higher risk of fractures In view of the above concerns, and the cursory mention of SGLT-2 inhibitors in the guidelines, we suggest that the whole drug treatment section of the guidelines should be looked at again. This should be done taking into consideration patients' safety and practical aspects of care such as multiple dosing and the need for self-monitoring. The section should fully incorporate all the current treatment options that have evidence of effectiveness including the SGLT-2 inhibitors in order to offer more options to clinicians and their patients. The guidelines should also reflect current best practice and other international guidelines such as the ADA/EASD guidelines. This will ensure that the application of research and shared practice is sustained and that the UK is not isolated in that regard.	inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
564	Diabetes UK	NICE	24	1.6.26	**First intensification of drug treatment** The inclusion of SGLT-2 inhibitors seems to be an after-thought. These agents are commonly used and have been NICE approved (NICE Technology Appraisals Guidance TA288 and TA315). Therefore, the section has to be looked at again and SGLT-2 inhibitors fully incorporated	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the

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					rather than just a reference to other guidance.	changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
565	Diabetes UK	NICE	26	1.6.31	**Second intensification of drug treatment** The inclusion of SGLT-2 inhibitors seems to be an after-thought. These agents are commonly used and have also been recommended in NICE Technology Appraisals Guidance TA288 and TA315. Therefore, the section has to be looked at again and SGLT-2 inhibitors fully incorporated rather than just a reference to other guidance.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
566	Diabetes UK	NICE	31	1.7.16	**Eye screening wording** We suggest changes in the wording. Currently: 'Arrange or perform eye screening at or around the time of diagnosis. Arrange repeat of structured eye screening annually'. Suggested change: 'Arrange or perform eye screening at or around the time of diagnosis. For people suspected of having undiagnosed Type 2 diabetes for a longer time – those symptomatic and/or with very high HbA1c – perform eye screening as soon as possible before initiating medication for blood glucose treatment. Arrange repeat of structured eye screening annually'	Thank for your comment. The advice of the diabetic eye screening programme was sought on these recommendations which have not been updated by an evidence review. The comment has been highlighted to the diabetic eye screening programme.

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					Even though this recommendation was not reviewed for this consultation, we consider the safety issues associated with worsening retinopathy that could result in sight loss as a consequence of intensive blood glucose treatment to be very serious. Therefore, we will entreat the group to seriously consider rewording the eye screening recommendation for clarity.	
567	Diabetes UK	NICE	General		• There is no mention of modified-release metformin, and when it should be considered. • There is no mention of bariatric surgery. There must be a reference to the NICE CG 189 to highlight bariatric surgery as a viable treatment option for some people with Type 2 diabetes • There is no mention of oral care. Given the fact that poor oral health can affect blood glucose control, and that poor blood glucose control can affect oral health, there should be guidance on oral health. We also suggest 'The role of oral care in Type 2 diabetes management' be added to the recommendations for research. This will help us better understand how to incorporate oral care into diabetes management.	Thank you for your feedback. The pharmacological management recommendations have been reconsidered by the guideline development group in the light of stakeholder consultation and metformin modified-release is now an option for initial therapy where standard-release metformin is contraindicated or not tolerated. A cross reference to NICE clinical guideline 189 has now been added at the end of the section on Dietary Advice within the guideline. Oral care was not identified as an area to be covered within this iteration of the type 2 diabetes guideline. Therefore it is not possible to offer any recommendations on this or potential research recommendations.

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413	Education for Health	NICE	11	General	We fully endorse the comments made about personalised care and home blood glucose monitoring	Thank you for your feedback.
414	Education for Health	NICE	12	General	Repaglinide after metformin :We cannot support the choice of this treatment especially when viewed in the context of the aims stated on page 11and in section 1.1.1 – these aims are contradictory	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
415	Education for Health	NICE	13	1.2.1	The education elements will need to be expanded to meet demand	Thank you for your comment. Education was not prioritised within the guideline for update. This decision was taken following a workshop conducted with stakeholders during the scoping of the guideline and stakeholder consultation. It may be possible to address this area in a future iteration of the guideline.
416	Education for Health	NICE	14	1.2.4	How would this standard be measured?	Thank you for your comment. It is not within the remit of the clinical guideline on type 2 diabetes to set audit standards to be measured. These can be drawn from the NICE Diabetes in adults quality standard.
417	Education for Health	NICE	16	1.4.3	Is this monitoring advice in line with current NICE advice on hypertension monitoring which	Thank you for your comment. This section of the type 2 diabetes guideline was not prioritised for

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					includes home BP monitoring	update following the stakeholder workshop and stakeholder consultation during the scoping phase. The recommendations have been brought forward from the previous iteration of the guideline unchanged. As no new evidence reviews have been conducted, it is not possible to make any changes to these recommendations. The NICE guideline (CG127) on hypertension from 2011 did not include people with diabetes; therefore the recommendations on blood pressure monitoring which appear in the type 2 diabetes continue to stand. However, the suggestion has been logged and will be taken into account when the guideline is next considered for update.
418	Education for Health	NICE	22	General	This algorithm is unworkable and ill advised. It is not patient focused and comes with too many potential risks. This needs serious reconsideration as it threatens to cause patient harm and harm to the reputation of NICE.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
419	Education for Health	NICE	24	1.6.26	Newer therapies are already being used, especially by more experienced practitioners.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2

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					NICE has a duty to offer clear guidance as to where they sit in an algorithm that recognises the patient as being central to this update. A suitable example of this approach would be the ADA/EASD guideline	inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
420	Education for Health	NICE	25 -26	General	Too complicated and confusing. See ADA/EASD for advice.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
421	Education for Health	NICE	General	General	Some really workable ideas but this guideline is completely let down by the pharmacological section which takes no heed of the need to simplify medication regimens, simplify guidance for health care professionals which recognises the role of newer therapies and minimise complications	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice

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						around which pharmacological interventions are appropriate for consideration.
422	Education for Health	Full	General	General	As above. Suggesting that stake holders familiarise themselves with the economic model used for the pharmacological component of the guideline seems to suggest that this was the basis for the guideline being written as it was. The level of concern that has been expressed about the draft pharmacological guideline might underline to the GDG that economics are not the sole consideration here and neither should they be.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
327	Faculty of Pharmaceutical Medicine	NICE	15	General	The intensification scheme favours complicated treatment combinations (3 oral drugs) that are known to be effective for a limited time due to disease progression. GLP-1s which provide added benefits on glycaemic control, weight and hypoglycaemia are not well covered. Combination of GLP-1 and insulin, (free combination or fixed combination products) are not considered as a way to enhance glycaemic control, and limit hypoglycaemia risk, thus making insulin treatment more tolerated. SGLT2s are not integrated in the scheme either. In general, the recommendations do not take adequately into consideration the benefits that new treatments can offer (simpler treatment options, mitigation of insulin-related side effects, weight benefit)	Thank you for your feedback. At second intensification, triple oral drug combinations have been recommended, alongside starting insulin-based treatments. Combination therapy with GLP-1 mimetics and insulin is recommended with specific starting and stopping rules. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate.

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328	Faculty of Pharmaceutical Medicine	NICE	56	4	The sentence has been closed with two periods	Thank you for your feedback. The text has been amended.
329	Faculty of Pharmaceutical Medicine	NICE	64	20	The Abbreviation has been mentioned as ACE1 instead of ACEI	Thank you for your feedback. The text has been amended.
330	Faculty of Pharmaceutical Medicine	NICE	66	17, 20, 36	The Abbreviation has been mentioned as AR2B instead of A2RB	Thank you for your feedback. The text has been amended.
331	Faculty of Pharmaceutical Medicine	NICE	70	25	The title included diuretic too but no data has been mentioned below with regard to BP reduction by diuretic	Thank you for your feedback. This section has not been updated by an evidence review following the stakeholder workshop and stakeholder consultation during the scoping phase and has been carried forward from the previous version of the guideline that was published in 2009. Data on diuretics in relation to blood pressure and the improvement of vascular outcomes can be found in section 6.3.3 in the full guideline.
332	Faculty of Pharmaceutical Medicine	NICE	70	30	The spelling of Verapamil has been mentioned as Verapamill	Thank you for your feedback. The text has been amended.
323	Faculty of Pharmaceutical Medicine	NICE	General	General	Technical issues of fundoscopy e.g. venous reduplication are beyond the understanding of most doctors.	Thank you for your feedback.

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324	Faculty of Pharmaceutical Medicine	NICE	General	General	There is only passing reference to lipid management: this is a big part of management of type 2 diabetes in clinical practice and surely would merit more space in the guideline.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence on lipid management in people with type 2 diabetes. There is recently published guidance on lipid modification (CG181) that is cross referred and includes recommendations on the management of lipids in people with type 2 diabetes. The NICE pathways online tool is the main interface through which clinicians now access NICE guidance and will hopefully enable easy navigation between type 2 diabetes and all pieces of related NICE guidance.
325	Faculty of Pharmaceutical Medicine	NICE	General	General	The guideline is too big (it would benefit from the briefest of executive summaries) and too reliant on network-meta-analysis (a technique that not all are comfortable with). It is not clear who the target audience is.	Thank you for your feedback.
326	Faculty of Pharmaceutical Medicine	NICE	General	General	Hypoglycaemia is well noted that is a limiting factor for intensive glycaemic control. However, no mention has been made or no research has been proposed to assess whether available treatments that provide hypoglycaemia benefits (GLP-1s, or free/fixed GLP-1 and insulin combinations) may overcome this issue.	Thank you for your feedback. Research recommendations have been made on various treatment combinations and it is anticipated outcomes will include hypoglycaemia and other adverse events.
370	Foundation for Diabetes Research in Older	Full	General	General	The initial patient focus of the guideline should be commended and that testing and targets are useful/applicable to a large number of patients. However, the guideline does not provide	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised

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	People, Diabetes Frail Ltd				appropriate guidance to older patients who may have features of pre-frailty, frailty, housebound, care home residency, dementia or end of life! I This is an important omission, a missed opportunity and in my view, unacceptable in this modern era of equitable treatment for all. The prevalence of these features and characteristics demand more attention by the Guideline Development Committee. I would refer the Committee to the recently released IDF Global Guidance on Managing Older People with Type " Diabetes who provide a rationale for prescribing for older people based on patient categories relating to whether or not they are independent or dependent with goals and targets appropriately defined. Your insistence on a HbA1c less than 7.5% (old units) for most treatment options is UNSAFE in many older people and predisposes them to unnecessary and often dangerous hypoglycaemia, without the evidence of known vascular benefit. When all international diabetes guidelines are stressing the importance of individualised approaches, treatment decisions based on comorbidities, life expectancies, and frailty/disability, I am concerned that the Committee has not felt it important to stress similar views.	target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Specifically, recommendation 1.6.9 suggests relaxing the HbA1c target on a case by case basis considering the frail or elderly among other factors. Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
371	Foundation for Diabetes Research	Full	General	General	I am not convinced that the proposed algorithm is being applied consistently throughout the guidance and unfortunately, I feel that this undermines the initial patient centred approach.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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	in Older People, Diabetes Frail Ltd				It appears to follow a cost minimisation strategy which I believe is not in line with NICE Guideline development processes nor the principles agreed under PPRS between the Department of Health and the ABPI.	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
372	Foundation for Diabetes Research in Older People, Diabetes Frail Ltd	Full	General	General	Considerations of patient safety, functional category and level of independency, physician choice as well as patient choice are essential elements which should play a role when embarking on a treatment pathway - the current draft of CG87 does not consider this) and if implemented in its current form, it could be viewed as a backward step for diabetes patient centred care. I might go as far to say that the new draft CG87 is at conflict with the NHSE/Nice Medicines Optimisation Strategy which encourages adopting a patient centred treatment approach, potentially using more branded medicines if appropriate.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
373	Foundation for	Full	General	General	At the Foundation we are of very much of the view that metformin should be seen as 'Usual'	Thank you for your feedback. The guideline development group has reflected on the clinical

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	Diabetes Research in Older People, Diabetes Frail Ltd				choice as first line glucose-lowering therapy, but as recommended in the IDF Guidance for older people mentioned above, other therapy classes should be considered as alternatives to metformin depending the individualised approach. This is also consistent with the evidence based approach by American Diabetes Association/ European Association for the Study of Diabetes.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
374	Foundation for Diabetes Research in Older People, Diabetes Frail Ltd	Full	General	General	We accept that extra caution in the use of sulphonylureas is important particularly in older people who may have additional risk factors for hypoglycaemia. However, I am very concerned about the position occupied by repaglinide and pioglitazone in the revised recommendations since they are not as routinely used in the UK as other agents and the side effects or other limitations of these products should be appropriately and robustly considered in the revised CG87 particularly in relation to older patients – unfortunately, this is currently not the case. It is true that glinides are recommended as an	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A

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					option for first line therapy in older patients with type 2 diabetes (see the recent IDF Global Guideline - Managing Older People with Type 2 Diabetes) and that this was centred around evidence of reasonable efficacy and tolerability to that of SU's **and** the idea that those who may skip meals, or have postprandial hyperglycaemia or have erratic eating habits might have a lower risk of hypoglycaemia using a glinide. However, where diabetes self-management is expected, older patients would still have to be in relatively good health, have features of pre-frailty only, and have little evidence of memory disorder or cognitive impairment. It was also pointed out that drug-drug interactions were a risk with many of the medications taken by older people such as salicylates, NSAIDS and certain antibiotics. Where moderate to severe frailty is present or dementia has been diagnosed, the used of glinides in older people could only be justified on the basis of their single dose/short-acting profile that may reduce the hypoglycaemia potential, if there is a robust carer-support package present that ensures that adherence is strict and the risk of inadvertant hypoglycaemia is minor. In care homes, such support is theoretically possible but in several of our previous studies and audits we have shown many of the shortfalls in diabetes care in care homes and that hypoglycaemia is a major concern.	footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. However, as per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

Type 2 diabetes (update)

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375	Foundation for Diabetes Research in Older People, Diabetes Frail Ltd	Full	General	General	In regard to DPP4 inhibitors, I question whether all the currently evidence was reviewed for all in this class? It would be helpful if NICE stated which of these were reviewed for mono, dual or triple therapy (as per the full guideline) to avoid the risk of off-licence prescription. As you are aware, DPP4 inhibitors are not all the same, for instance in terms of licence indications, and therefore this should be considered before cost. I believe the statement on "lowest acquisition cost" should be removed as this is a confusing statement to clinicians and may mislead clinicians in their treatment decision-making. The importance of DPP4 inhiibitors in the modern management of an ageing population of people with diabetes has been underestimated – their excellent tolerability, minimal risk of hypoglycaemia, once daily dosing and use in a wide range of renal functional levels makes it an alternative approach to metformin as a first line therapy.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

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916	Hazelwood Group Practice, Warwickshire North	Full	13 ,14, 15	 appendix 2	Why do the guidelines only offer standard release metformin, many patients who are unable to tolerate standard release preparations cope well on the modified release form? Metformin MR is available at low acquisition costs compared to e.g. DPP4 so omission of this makes little sense to me	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
675	Health Innovation Network (South London Academic Health Science Network)	NICE	13	1.11	Many individuals may have had type 2 diabetes for a significant time period prior to diagnosis and have already developed complications such as nephropathy or retinopathy. Therefore initiating therapy should be individualised. Metformin use should be encouraged very early soon after diagnosis for some patients and not necessarily based on worsening Hba1c.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
677	Health Innovation Network (South London Academic Health Science	NICE	13	1.11	In line with the NICE Quality Standard 6, statement 3, please incorporate care planning into the guidance.	Thank you for your feedback. The guideline emphasises that care should be tailored to individual needs and that co-morbidities should be considered (which will include complications). Annual review is highlighted at several points in the document, including structured education with annual reinforcement and review.

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	Network)					
678	Health Innovation Network (South London Academic Health Science Network)	NICE	13	1.11	Although the guideline states we should be individualising care, providing one algorithm for the management of hyperglycaemia for all age and ethnic groups does not support individualisation of care.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
679	Health Innovation Network (South London Academic Health Science Network)	NICE	19	1.67	Metformin use should be encouraged very early soon after diagnosis for some patients not necessarily based on worsening HbA1c. The United Kingdom Prospective Diabetes Studies show reasons for early tight control. The guideline also suggests inappropriately waiting for HbA1c levels to rise to 58mmol/mol prior to intensifying therapy early in the type 2 diabetes pathway.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group purposely did not select a drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) as it was considered too low and inappropriate for most people as the condition progresses. In addition, the group considered the natural fluctuating error observed in HbA1c measurements of about 2 mmol/mol (0.2%). Recommendation 1.6.5 (NICE version) promotes individualised target setting "*Involve adults with type 2 diabetes in decisions about*

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						their individual HbA1c target". The recommendations and algorithm have been amended to place an increased emphasis on individualised care and choice around targets and which pharmacological interventions are appropriate for consideration.
680	Health Innovation Network (South London Academic Health Science Network)	NICE	22	1.6.18	The guidance on when metformin is contra-indicated is very helpful. There should be similar statements for all of the newer agents to support individualising care. For example with pioglitazone, those who have heart failure, have a history of bladder cancer or at higher risk of fractures	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
681	Health Innovation Network (South	NICE	22	1.6.19	The use of metformin modified release tablets in line with the 2009 guidance has supported a significant number of patients to maintain the benefits of metformin therapy without the gastro-	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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	London Academic Health Science Network)				intestinal side effects previously experienced with standard release preparations. Why is modified release metformin no longer considered as an option when standard release metformin is not tolerated?	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
682	Health Innovation Network (South London Academic Health Science Network)	NICE	22	1.6.19	Adherence with repaglinide three times a day is likely to be low. In practice we have seen poor adherence to the lunchtime dose of metformin resulting in a change to twice daily dosing. This flexibility to achieve maximum HbA1c reductions from repaglinide therapy may not be an option	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
683	Health Innovation Network (South London Academic Health Science Network)	NICE	22	1.6.19	Repaglinide is not licensed with other oral hypoglycaemic agents apart from metformin. Suggesting for those who cannot tolerate standard release metformin to start therapy with repaglinide and then to change therapy to either pioglitazone, sulfonylurea or DPP-4 inhibitor to be able to progress through the pathway is questionable. Type 2 diabetes is a progressive condition meaning over time, the majority (if not all) patients will progress to	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence

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					needing more than monotherapy. This would mean that all patients on repaglinide as a first line agent will need therapy stopped and changed to an alternative at some point. Cost implications including the cost of increased healthcare consultations, increased HbA1c testing, costs of delaying therapy whilst monotherapy is changed, stabilised and then a second agent added, and the potential cost of side effects and non-compliance from changing therapy need to be taken into account.	available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
684	Health Innovation Network (South London Academic Health Science Network)	NICE	23	1.6.23	Starting dual therapy causes problems as there is an inability to identify which drug has caused a side effect resulting in both being stopped and cautiously re-challenged in patients who agree to this. A significant number of patients may refuse to be re-challenged which would mean both drug therapies are unable to be used. In practice, this will be making life much more difficult for the person with Type 2 diabetes.	Thank you for your feedback. The recommendation has been simplified and a footnote added that at first intensification for repaglinide, drug must be stopped and dual therapy with other oral antidiabetic drugs be introduced in a *stepwise* manner, checking for tolerability and effectiveness of each drug.
686	Health Innovation	NICE	24	1.6.26	Please incorporate SGLT-2 inhibitors into the guidance rather than referring to other NICE	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2

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	Network (South London Academic Health Science Network)				guidance covering these medications.	inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
687	Health Innovation Network (South London Academic Health Science Network)	NICE	26	1.6.31	Not all GLP-1 analogues are licensed with basal insulin. Exenatide prolonged release (Bydureon) is not licensed with basal insulin. Recommendation is to add 'Licensed GLP-1 analogues combinations should be used'	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
688	Health Innovation Network (South London Academic Health Science Network)	NICE	26	1.6.31	Please incorporate SGLT-2 inhibitors into the guidance rather than referring to other NICE guidance covering these medications.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
69	Health	NICE	27	1.6.3	We welcome the continued recommendation for	Thank you for your feedback.

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0	Innovation Network (South London Academic Health Science Network)			4	conventional human (isophane) insulin first line in Type 2 diabetes and refer the group to a recent review undertaken by the London Medicines Evaluation Network http://www.medicinesresources.nhs.uk/en/Communities/NHS/SPS-E-and-SE-England/LNDG/London-Wide-Reviews/First-line-insulin-therapy-choice-in-type-2-diabetesNPH-isophane-insulin-or-a-long-acting-insulin-analogue-insulin-detemir---6355062066/	
685	Health Innovation Network (South London Academic Health Science Network)	NICE	General	General	Safety concerns exist regarding pioglitazone and remain used with extreme caution in many centres for concern over upper limb fracture and bladder lesions. It also causes significant weight gain. These side effects should be highlighted and other alternatives should be considered first. The guidance appears to place undue weight to cost saving, whilst reducing the importance for personalisation of care.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm. The recommendations and algorithm have been simplified and amended to place an increased

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						emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
689	Health Innovation Network (South London Academic Health Science Network)	NICE	General	General	Given the comments above, we suggest that the whole drug treatment part of the guidelines should be reviewed. Suggesting that one pathway for the management of hyperglycaemia can be used for all groups without taking into account co-morbidities, current macro and microvascular complications and frailty is not appropriate.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
809	Janssen	Appendix F : Full Health Economics	13-15; 21;	Treatment Algorithm; 40-45; 12-	Diabetes is a challenging area in which to conduct indirect comparisons and network meta-analyses. While there is a great deal of information, the evidence is not evenly distributed across therapies and lines of therapy. As a result, the methods used in network meta-analyses are evolving particularly regarding the	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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		Report ; NICE Update CG	22	15	use of Bayesian approaches. The NICE analysis team has done a great deal of work to draw together a complex evidence base, however, Janssen would like to highlight a few specific issues with the network meta-analysis that are typical of the challenges seen with diabetes. • Repaglinide data: The recommendation of repaglinide early in therapy may not be justified by the data. In particular, the sulfonylurea and placebo arms of the included studies show HbA1c results that are not consistent with other studies in the same analysis, suggesting possible heterogeneity, and are based on very limited data with some noticeable issues (such as dropout). Whilst the analysis does use random effects, there are not sufficient data to robustly estimate the random effect for those particular comparisons and there is a marked risk of unmeasured/unaccounted heterogeneity as a result. • Inconsistent dropout: The results may be affected by a very large risk of placebo dropout (max. 67%), as well as an inconsistent risk of dropout across studies. To inform the pharmacotherapy treatment	The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group also has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. Repaglinide data: Dropouts in repaglinide studies are not obviously different from those in others. In the critical 12 month analysis, HbA1c reductions in the sulfonylurea arms of repaglinide studies (range: -0.5 to -1.1) are entirely consistent with those seen in the rest of the sulfonylurea evidence base (range: -0.3 to -2.03). Network meta-analyses of randomised studies are preferred as it allows retention of focus on differences between randomised cohorts. The selection of and limitations within the UKPDS OM1 were fully considered by the guideline development group (see appendix F 3.1 and 5.2.2). The guideline development group reviewed and approved the baseline data values used. The 6 month data selection period was utilized to allow for lags in data recording. It was assumed the vast majority of people with type 2 diabetes

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					algorithm and recommendations within the draft clinical guideline, NICE has used the original UKPDS health outcomes model, OM1. This was developed based on treatment of newly diagnosed patients with T2DM in the 1990s and is no longer reflective of UK practice. Patterns of care have changed significantly since the RCT was conducted and this could have an effect on the calculated risk factors. To account for the patient population no longer suitably reflecting current clinical practice, NICE has used THIN data to inform the UKPDS OM1, to model long-term outcomes in different patient groups. It is well established that this is an acceptable approach to account for clinical practice evolution. However, Janssen have reviewed the analysis that was conducted and believe that there are some elements of the analysis that may have led to an inappropriate patient group selection and thus incorrect baseline characteristics. The results appear inconsistent with published THIN data [Bennett et a. (2014)]. A possible reason for this inconsistency is that data were selected for the point at which people were first prescribed anti-diabetes mediation other than insulin, with measurements recorded closest to the prescription date (± 6 months). Janssen suggest recording HbA1c +6 months following treatment initiation will likely include the HbA1c-lowering	would have their Hba1c measured and recorded close to the data of their first prescription. Only data for initial therapy are comparable, as the NICE model selected first and second intensification data based on set disease durations. Bennett et. al. (2014) contained a number of limitations that could result in different values. Bennett et. al. (2014): - had shorter disease durations at each therapy level - limited their data to a 4 year period, meaning people who were well controlled over a longer period would be excluded - appears to have inconsistent age and gender data across therapy levels - did not adjust for extreme data values - excluded people on DPP4 inhibitors. Only direct NHS costs are considered by NICE. Costs associated with severe hypoglycaemia were detailed in appendix F 3.9.4. Utility loss associated with the fear of hypoglycaemia was discussed in appendix F 3.10.4. The health economic model considered those outcomes priortised as critical and important by the guideline development group (see guideline 8.4.2). Including other outcomes would have seriously limited the number of treatment options

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					effect of the treatment. As such, this may explain why patients with more intensive therapy have lower HbA1c levels, a conclusion that is inconsistent with currently available data. The risk of hypoglycaemia with SU and insulin secretagogues is higher than with any other oral therapy, particularly in older patients and those with impaired renal function. Data from 2008 suggest that more than 5,000 patients each year experience a severe event caused by their SU therapy which will require emergency intervention. Hypoglycaemia has a substantial clinical impact, in terms of mortality, morbidity and quality of life. The cost implications of severe episodes—both direct hospital costs and indirect costs— are considerable: it is estimated that each hospital admission for severe hypoglycaemia costs around £1,800. A severe hypoglycaemic episode is extremely frightening for the patient and can result in a loss of trust between the patient and the healthcare professional. Hypoglycaemia and fear of hypoglycaemia can limit the achievement and maintenance of optimal levels of glycaemic control (Amiel et al, 2008). It appears such additional resource use has not been considered within the cost-utility analyses that inform the pharmacotherapy treatment algorithm.	that could be compared.

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					Janssen believes that these sources of bias and omission of data within the network meta-analysis and cost-utility analysis could potentially count towards the lack of consistency between the finding within the overall cost-effectiveness analysis and general findings in clinical practice. This may lead to a lack in consistency between the pharmacotherapy recommendations and treatment algorithm compared with the rest of the updated clinical guideline. Lastly, Janssen appreciates that glucose control remains a key clinical outcome in the management of patients with type 2 diabetes. However, Janssen believe that insufficient focus has been placed on management of secondary outcomes within the development of the treatment algorithm. Clinical indicators, such as QOF, are based on NICE guidance so it is imperative the guidelines are based on what is in the best interest of patients, rather than being skewed by what is most cost effective driven by acquisition cost. Currently the OM1 economic model only accounts for a select number of outcomes namely, HbA1, hypoglycaemia, discontinuation rates due to AEs and weight, while other outcomes such as systolic blood pressure and nephropathy are omitted. Janssen wishes to understand as to why outcomes considered previously as indicators of success	

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					in the treatment of diabetes have not been considered within the cost-effectiveness analysis?	
806	Janssen	NICE	13 - 15	Treatment algorithm	The proposed guideline recommends individualised care; however, the pharmacotherapy treatment algorithm does not appear to support personalisation of pharmacological intervention. There is no reflection of the clinical decision making process such as consideration of patient risk of hypoglycaemia and the necessity for blood glucose monitoring, measurement of renal function, body weight, or baseline HbA1c, or patient choice as well as associated costs within the algorithm. The use of the word "contraindicated" does not reflect these patient issues. Janssen suggest that it would be more appropriate to use 'Contraindicated or not preferred' at the decision point rather than 'Contraindicated' alone. A consensus group meeting, including diabetologists, GPs and nurses, chaired by Janssen on 24th February 2015, concluded as a result of the way in which the NICE guidelines may be applied locally, patients may end up following a strict pathway through the algorithm and attempt treatment with each medication in turn. This could lead to patients receiving inappropriate medication and a protracted wait for the most appropriate medicine for each	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					patient. As one of the consensus group noted – '*we want to give the right treatment the first time'* [Janssen (2015]). Delaying access for patients to newer anti-hyperglycaemic agents in the treatment paradigm could adversely affect achievement of improved long-term outcomes. Early successful control of both blood glucose and also comorbidities associated with type 2 diabetes; e.g. weight change and increased blood pressure can make a marked difference to long-term outcomes [Deed et al (2012)]. Therefore, Janssen would request that NICE readdress the pharmacotherapy recommendations and treatment algorithm to emphasise the importance of treatment decisions based on individual needs of the patient.	
807	Janssen	NICE NICE Final Scope, November 2012	13 -15; 21; 22	Treatment Algorithm; 40-45; 12-15	The draft guideline is inconsistent with Technology Appraisals (TAs) of newer products, e.g. SGLT-2 inhibitors (TA288, TA315). The consensus group believe that recommendations from the TAs for SGLT-2 inhibitors should be incorporated into the pharmacotherapy recommendations and treatment algorithm. The final scope of the draft clinical guideline clearly outlined: *"5.1.2 NICE guidance to be incorporated* *This guideline will incorporate the following NICE guidance subject to a technology*	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.

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					appraisal review proposal agreement: ➢ *Dapagliflozin in combination therapy for the treatment of type 2 diabetes (ID427)* ➢ *Canagliflozin for type 2 diabetes mellitus (ID554)"* Although it is acknowledged that the prescribing of SGLT-2 inhibitors was not updated by an evidence review as part of the clinical guideline update, Janssen believe that the findings of the TAs for the SGLT-2 inhibitors should be made appropriately clear throughout the guideline, particularly within the pharmacotherapy recommendations and treatment algorithm. It was suggested by the Consensus Group that a single point of reference for the generalist reader of the clinical guidelines is required. Reference boxes detailing where to find additional information do not allow for a full understanding of where a product should sit within the treatment algorithm and may be missed, potentially leading to sub-optimal treatment choices with adverse implications on health outcomes. Janssen would like to understand the rationale for inserting reference boxes to the latest TAs for the SGLT2 inhibitors, rather than incorporating them into the treatment algorithm and pharmacotherapy recommendations directly as per the TAs recommendations?	

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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808	Janssen	NICE	13 -15; 16	Treatment algorithm; 3-9	It was concluded by the consensus group that most generalist practitioners will refer to the pharmacotherapy treatment algorithm as a main point of reference; assuming that the general position of the clinical guideline as well as the pharmacotherapy treatment recommendations are accounted for within it. Therefore, it is important that the treatment algorithm reflects the entirety of the updated clinical guideline and not only the cost-utility analysis conclusions. Following the consensus group meeting, it became apparent that the complexity of the pharmacotherapy treatment algorithm will make the guidelines difficult to implement. Concern was raised that practitioners within primary care may find it difficult to follow the proposed guidelines particularly in the case of more complex patients (second intensification). This will result in an increased number of referrals to secondary care, which goes against the ambition of the NHS Constitution. The consensus group felt strongly that therapeutic decisions should be made on the basis of patient preference, HbA1c, weight, blood pressure, renal function and risk of hypoglycaemia and other adverse events. Thus, would NICE also consider the phrase 'Patient preference following discussion of benefits and harms' to be applicable at each decision point,	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The recommendations and algorithm have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					rather than restricted to one decision point and should be highlighted at the top of the pharmacotherapy treatment algorithm? The use of any medicine in patients with Type 2 diabetes must balance the glucose-lowering efficacy, side-effect profiles, anticipation of additional benefits, cost, and other practical aspects of care, such as dosing schedule and requirements for glucose monitoring. Encouragement to use the cheapest agent within each class can have negative consequences for patients, in that they are potentially denied the most appropriate treatment. Personalised care is the current focus of Type 2 diabetes management both internationally and within the NHS as reflected by the EASD/ADA position statement and the House of Care model, as explained in point 6 below. Janssen wishes that NICE would consider adding more emphasis on selecting medications based on patient characteristics. For example, by including the 'pros and cons' of each class as per the ADA/EASD position statement, supporting more informed patient centric decision making. Lastly, there is an apparent overemphasis in the algorithm of the patient group who cannot tolerate metformin IR (immediate release), and the number of pages across which the	

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					pharmacotherapy treatment algorithm is displayed. Would NICE consider simplifying the algorithm to one or two pages and including metformin SR (slow release) as an alternative for when metformin IR is not tolerated as recommended in the current guidelines (CG87)?	
810	Janssen	NICE	13 -15; 16	Treatment algorithm; 3-9	While the general consensus of the updated clinical guidelines reflect current NHS policy, commitments and legislation focussing on individualising care and improving outcomes, the proposed pharmacotherapy treatment algorithm and associated recommendations appear to go against aspirations set out in the NHS Constitution which is to provide high quality person-centred coordinated care (also described by the House of Care model), encouraging the best use of NICE approved medicines. The way in which the recommendations for SGLT-2 inhibitors are currently represented in the pharmacotherapy recommendations and treatment algorithm has the significant potential to limit use of these NICE approved medicines, which is not in the spirit of the constitution. Therefore, Janssen would request that NICE readdress the pharmacotherapy recommendations and treatment algorithm to include such NICE approved medicines in line with their recommendations. The 5-year forward view represents the shared view of the NHS' national leadership, and	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. **Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.**

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					reflects an emerging consensus amongst patient groups, clinicians, local communities and frontline NHS leaders to drive quality care and reduce variation and inequities. The clarity of the guideline underpins decision making and is therefore key to both variation and reducing inequalities. Again, therefore, Janssen would request that NICE readdress the pharmacotherapy recommendations and treatment algorithm to emphasise the importance of treatment decisions based on individual needs of the patient. Action for Diabetes 2012 in their state of the nation report emphasised the importance of primary care in managing the disease. Janssen would like to highlight that the draft clinical guideline update appears to inadvertently encourage management in secondary/ specialist care contrary to the general direction of health policy and the management of long term conditions. Janssen feel that greater clarity should be added to ensure care provision is commissioned and delivered in the right setting.	
805	Janssen	NICE	General	General	Janssen is pleased to see that the overall consensus of the draft NICE clinical guideline update is that personalisation of care is necessary, balancing the benefits of glycaemic control with its potential risks, and taking into account individual patients' comorbidities. However, it appears that the proposed guideline	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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					differs considerably from existing guidelines (Clinical Guidelines 66 & 87) in a number of areas where there is little or no change to the evidence base, e.g. use of repaglinide if metformin unsuitable, removal of stopping rules from existing guidelines, and use of acarbose. Janssen would like to understand this apparent inconsistency from previous guidelines. The general consensus of the draft guideline is that of individualised care, which also coincides with the latest position statement issued by EASD/ADA (Inzucchi, et al 2015); however the recommendations and treatment algorithm relating to pharmacotherapy do not appear to reflect this. Janssen would like to understand this inconsistency within the draft guideline and would be grateful for a clear explanation from NICE.	pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
109	Kidney Research UK	NICE	General	General	This new guidance contains little information on the management of nephropathy in T2DM, but rather cross-references the reader to recent NICE CKD guidance. This is unfortunate since the NICE CKD guidance does not contain a diabetes guidance section per se, but rather the diabetes guidance is dispersed throughout the document. It is therefore unfortunate that this NICE T2DM guidance does not synthesise information on nephropathy in diabetes into a coherent, single set of guidance, thus encapsulating the whole information for the	Thank you for your feedback. NICE antitipcates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. This function links all related NICE guidance on a topic area and should assure quick navigation between recommendations on type 2 diabetes and chronic kidney disease.

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					casual reader and emphasising the key importance of nephropathy in T2DM.	
255	Leeds North CCG	Full	11	19	If standard release metformin isn't tolerated then surely the next step would be M/R metformin rather than repaglinide which requires self-monitoring BG..	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
252	Leeds North CCG	NICE	12	7	Choice of repaglinide. Prescribers aren't familiar with it. More are used to Gliclazide etc. Its significantly more expensive and patients find it difficult to tolerate the GI side effects .It also requires multiple dosing with main meals so isn't practical to prescribe in the elderly who will forget to take it. It is only licensed for monotherapy or in combination with metformin so it's impractical to add in further treatment (you suggest switching it!). Not practical.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
256	Leeds North CCG	Full	13	1	The algorithm looks busy and is complicated to follow. Repaglinide takes you to a dead end whereas if you used gliclazide or other SU you could then add pioglitazone or a DDP-4 inhibitor or a GLP-1. Instead you are suggesting stopping the repaglinide and substituting for one of those agents. It isn't practical and most prescribers will	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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					struggle to mange this.	The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
257	Leeds North CCG	Full	13	2	'Choose the DDP-4 inhibitor with the lowest acquisition costs'. Some DDP-4 inhibitors are licensed for triple oral therapy and some are not. This needs to be taken into account and reflected in the pathway.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
258	Leeds North CCG	Full	14	1	You need to state that adequate time must be given to allow the new treatment to work and most people wait a min of three months before rechecking HbA1c to see if a treatment has worked (+/- SMBG readings).	Thank you for your feedback. The guideline development group has recommended that HbA1c is measured every "*3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy*" and is reflected in the updated algorithm.
259	Leeds North CCG	Full	14	1	Algorithm too complicated to look at and follow	Thank you for your feedback. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which

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						pharmacological interventions are appropriate for consideration.
260	Leeds North CCG	Full	15	1	Algorithm too complicated to look at and follow	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
253	Leeds North CCG	NICE	18	11	Rather than just say 'do not offer antiplatelet therapy', could this be strengthen to include stopping it in existing patients who were prescribed it in the past.	Thank you for your feedback. The guideline development group considered that making a specific recommendation to stop existing therapies may cause some confusion in the case of secondary prevention. Therefore, the group thought that the strong "do not offer" recommendation should reasonably indicate to healthcare professionals to consider reviewing patients' existing therapies as appropriate.
254	Leeds North CCG	NICE	19	7	Consideration should be given to home blood glucose readings in conjunction with HbA1c. Often home self monitoring BG readings show points in the day where glucose levels dip and the patient is hypoglycaemic, but their overall HbA1c may be within limits or high. This would prompt an increase in e.g. repaglinide dose, but this could cause hypos at certain points in the	Thank you for your feedback. Recommendation 1.6.3 provides alternative options for estimating trends in blood glucose control including quality-controlled plasma glucose profiles.

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					day. Therefore home BGM shouldn't be ignored.	
261	Leeds North CCG	NICE	26	3	Choice of GLP-1 should also take into account that those who need help to from a carer or HCP to inject administer should consider a long acting weekly GLP-1.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
262	Leeds North CCG	Full	General	General	The treatment choices and algorithms differ so much from current NICE guidance that more prescribers will struggle with such a huge change. They are only just getting to grips with the current algorithms.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased

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						emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
263	Leeds North CCG	Full	general	general	Feedback from prescribers is that the current algorithms are difficult to use as they are in electronic 'click on the box' versions which assumes you will have an electronic version of the guidance open when making a decision. It doesn't enable you to see the algorithm choices on one page and therefore isn't suitable for printing out for display. I think unless you also produce a more simplified paper version that can be printed, people will struggle to remember the combinations, especially as they are different drug choices compared to previous.	Thank you for your feedback. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
408	Leeds Teaching Hospitals Trust	Full	13	Figure 1	There are some inconsistencies when addressing the patient centred approach with concerns in relation to the choice of two hypoglycaemic agents, namely pioglitazone and repaglinide. The recommendation to use pioglitazone and repaglinide as second line therapy, or first line instead of metformin, appears to be driven by the need for short term cost minimisation rather than hard scientific facts.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular

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						caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. The health economic modelling considered both costs and quality of life impacts of long-term complications (in part driven by changes in HbA1c), hypoglycaemia rates, treatment-related weight changes as well as drug acquisition and management costs (see 8.4.3 in the full guideline).
411	Leeds Teaching Hospitals Trust	Full	15	Figure 3	In relation to the relatively new class of hypoglycaemic agent, the sodium glucose linked transporter (SGLT)-2 inhibitors, there is a lack of clarity for their use. To refer to this class with the expression "beyond the scope of these guidelines" is not helpful and will almost certainly create unnecessary confusion.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
409	Leeds Teaching Hospitals Trust	Full	20	Point 50	The recommendation to use repaglinide treatment suffers from the lack of robust clinical evidence backing such an approach. Compared with other hypoglycaemic agents, trials conducted with repaglinide are relatively small scale and this, together with the limited clinical use of this agent, questions the evidence-based approach for the recommendation. Admittedly, repaglinide is less likely to cause hypoglycaemia	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-

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					compared with a traditional sulphonylurea but the risk is still significant. Moreover, the need to take this agent 3-4 times a day creates difficulties with compliance, whereas the role of this agent in long-term glycaemic control is largely unknown. Also, the cardiovascular risk profile of repaglinide has not been appropriately studied and, to the knowledge of the group, there are no plans to conduct such trials in the future, in contrast to newer hypoglycaemia agents.	release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
410	Leeds Teaching Hospitals Trust	Full	21	Point 53	Whilst pioglitazone targets insulin resistance, the main pathophysiological mechanism in type 2 diabetes, treatment with this agent is associated with a number of side effects, including weight gain, heart failure and bone fractures. Pioglitazone may be suitable for selected patients with type 2 diabetes, but the widespread prescription will almost certainly increase morbidity and hospital admissions. Therefore, our group feels that ***routine*** use of pioglitazone as a second line agent in patients with type 2 diabetes is not safe and should not be encouraged.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest

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						acquisition cost). In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
407	Leeds Teaching Hospitals Trust	Full	General	General	A number of positive points emerge from the proposed guidelines, including the initial patient-centred care, importance of education, dietary advice and the clear guidance for self-monitoring of blood glucose. Moreover, it is reassuring that the guidelines recognised that agents in the sulphonylurea class are not suitable for all patients as second line therapy, further emphasising the importance of treatment selection according to the need of each patient. Also, the recommendations for the choice of long acting insulin are clear, safe and patient centred.	Thank you for your feedback.
412	Leeds Teaching Hospitals Trust	Full	General	General	We urge the Committee to reconsider the recommendations for pioglitazone and repaglinide in the final version of the guidelines. Also, more clarity is needed for the use of newer hypoglycaemic agents, particularly SGLT-2 inhibitors. We would like to stress that treating patients with diabetes should be based on careful evaluation of the clinical and social circumstances of each individual. Therefore, the choice of the hypoglycaemic class and the	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors,

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					sequence of the agents prescribed may differ from the recommended guidelines, a point that the Committee may wish to emphasise.	pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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						TA guidance.
708	Lilly UK	Full	22	20-24		
711	Lilly UK	Full	22	40-41		
707	Lilly UK	NICE	25 Section 1.6.29	_	GLP-1 RAs have been recommended only in combination with Metformin + SU only. This recommendation fails to take into account the fact that some GLP-1s are licensed for use in combination with any oral agents and may be used in clinical practice with drugs other than Metformin + SU. The guideline does not make any recommendations for use of GLP-1 RAs in combination with other oral agents.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations.
702	Lilly UK	Full	252 Section 8.4.15	25 -36		
706	Lilly UK	Full	252 Section 8.4.15	26-27		
709	Lilly UK	Full	254 Other consi		This section states that *"Based on the lack of research evidence on combinations of insulin-GLP1 mimetics, a strong 'only offer' recommendation was made to provide this treatment combination in a specialist care*	Thank you for your feedback. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics in combination with basal insulin were not identified at the cut off search date of June 2014. Any studies published

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			derations Page 250 Trade-off between benefits and harms		*setting"* and "*The GDG noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting"* GLP-1s have been used in clinical practice in combination with insulin since they were first launched and the SmPCs for most GLP-1s (including liraglutide, exenatide bd and lixisenatide) contain a summary of trial results in section 5.1 in combination with a basal insulin. This shows that the clinical evidence for use of insulin-GLP1 mimetics exists and should be a basis for allowing use.	after this date could not be included in this update. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations.
701	Lilly UK	NICE	26 Section 1.6.30 (BMI restrictions for GLP-1 receptor agonists)		It is not apparent why the BMI cut-off of ≥35kg/m^2 for the use of GLP-1 RAs has been retained from CG87. In the absence of a specific relationship between BMI and the GLP-1 RAs in terms of HbA1c reduction, there does not appear to be any justification for restricting the use of GLP-1 RAs to patients above a certain BMI.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

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703	Lilly UK	NICE	26 Section 1.6.30	_	Continuation rules for the GLP-1 RAs include targets for both HbA1c *and* weight. Data from the exenatide and liraglutide audits Thong et al (2014) shows that less than 30% of patients receiving liraglutide or exenatide achieved both HbA1c and weight reduction as specified in CG87, which shows that the continuation criteria are not being implemented in clinical practice. We suggest that change in HbA1c, reflecting the licensed indication (i.e. type 2 diabetes) should be the sole criteria for continuation of GLP-1 RAs, since the primary aim of treatment with GLP-1 RAs is to achieve glycaemic control, with weight loss and also very importantly, lack of weight gain being a desirable secondary outcome. Since GLP-1s do not cause weight gain, which in itself could be beneficial in type 2 diabetes, patients who experience improvement in HbA1c but do not experience weight gain should be permitted to continue their treatment.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
705	Lilly UK	NICE	26 Section 1.6.30 (BMI restrictions	_	If the BMI restrictions for use of GLP-1 RAs are retained in the final version of the NICE guideline, the provision in CG87 for downward adjustment of the BMI cut-off in non-European patients should be retained.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.

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			for GLP-1 receptor agonists)			Consideration for adjusting BMI levels based on ethnicity has been carried forward from the recommendation in CG87.
710	Lilly UK	NICE	26 Section 1.6.31	_	It would be helpful to clarify if 'specialist care setting' refers to secondary care only or includes GPs who may be specially trained and equipped to carry our treatment initiation with insulin in combination with GLP-1 RAs. Currently, treatment initiation with injectables (insulins or GLP-1 RAs alone) is carried out in primary care by an increasing number of GPs who have been trained to do so. The initiation of GLP-1s in combination with insulin would be the next logical step in this process. In view of the drive to move patient care towards the primary care setting. It would seem appropriate to recommend that the GPs who have had specific training should be permitted to initiate GLP-1 RA treatment in combination with insulin, in line with licensed indication for the specific GLP-1 RA.	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
714	Lilly UK	Full	287 9.3.4	8	In response to Recommendation 83: The choice of PDE-5i should be made based on individual patient needs and not on acquisition cost alone.	Thank you for your feedback. The evidence review on the clinical and cost effectiveness of PDE-5 inhibitors showed little differences between individual drugs. While the guideline development group recognises that there are other factors in drug choice such as timing and

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						frequency of dose, given the limited evidence base, a generic recommendation considering contrainidications and acquisition cost was thought to be most appropriate. In addition, the recommendation contains the word "initially" to reflect that in clinical practice, drugs and doses are chosen but may be altered depending on the progress of the individual patient.
713	Lilly UK	Full	General	Figure 3 Pharmacological treatment algorithm – second intensification	The section of the algorithm that refers to switching patients from NPH insulin to analogue insulins needs an annotation referring to recommendation 66 of the guideline in order to clarify what circumstances may call for such a switch.	Thank you for your feedback. The algorithms have been simplified to a single A4 page and amended to include the circumstances in which NPH insulin should be switched to analogue insulins.
700	Lilly UK	NICE Full	General	General	Thank you for the opportunity to comment on the draft of the NICE type 2 diabetes guideline. NICE guidelines have an important role to play in providing guidance on the use of pharmacological treatment options in primary care. It is critical that these guidelines are	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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					consistent with current clinical practice within the NHS in England and Wales, failing which it is possible that the recommendations may not be useful for clinicians. Over the years, the treatment of type 2 diabetes in UK clinical practice has evolved so that choice of therapy is dictated by clinical judgement and individual patient needs. In order to reflect this, the NICE guideline should lay out the available treatment options at each level of intensification and leave the actual choice of treatment to the clinician (in line with ADA/EASD guidelines on type 2 diabetes), rather than specifying a highly prescriptive and rigid treatment algorithm. Similar concerns have also been highlighted in a recent critical analysis of the draft guidelines by O'Hare et al (Br J Diabetes Vasc Dis 2015; 15:xx-xx http://dx.doi.org/10.15277/bjdvd.2015.006).	The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
712	Lilly UK	NICE	General – positioning of GLP-1 RAs in the treatment pathw		The NICE guidance on liraglutide (TA203) and exenatide once-weekly (TA248) recommended the use of these agents as triple therapy in suitable patients (defined by BMI and the presence of other psychological/ medical problems/comorbidities) and as dual therapy in a more restricted population (patients who can't tolerate or have contraindications to the use of metformin, SUs, TZDs and DPP-4s). The current guideline updates and replaces both pieces of guidance but restricts the use of GLP-	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 (liraglutide) and NICE technology appraisal guidance 248 (exenatide prolonged-release). The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence, and not only the available licensed combinations. The guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1

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			ay for type 2 diabetes		1s to triple therapy only. Although GLP-1 RAs are used mainly as triple therapy in UK clinical practice, clinicians should have the option of prescribing a GLP-1 RA as dual therapy in a select group of patients as recommended in TA203 and TA248.	mimetics (exenatide or liraglutide) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG considered the long-term safety risks associated with the use of GLP-1 mimetics and the evidence from the health economic model and agreed that there was strong evidence that these dual therapy combinations were not cost effective and should not be recommended routinely. Hence, GLP-1 mimetics are only recommended at second intensification. The group also noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the

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						GDG chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from CG87.
334	Medtronic Limited	Full	23	9 (rec# 56)	In a large-scale international, multi-centre randomised controlled trial (RCT) comparing insulin pump therapy vs. multiple daily insulin injections (MDI) in type 2 diabetes mellitus, Reznik et al. recently reported statistically and clinically significant improvements in glycaemic control with insulin pump therapy compared to MDI, in patients selected as having continued poor control on MDI (n=331) (Reznik et al., 2014). Improved control with CSII was achieved without increased weight gain or hypoglycaemia, but with 20% less insulin dosage. This landmark study, published in the Lancet, provides robust evidence to demonstrate that insulin pump therapy is a safe and effective treatment option in a small subgroup of patients with poorly controlled type 2 diabetes who are on multiple daily injections. This confirms previously reported data from smaller RCTs and observational studies (e.g. Berthe et al., 2007; Leinung et al., 2013; Edelman et al., 2010; Parkner et al., 2008). The authors suggest several mechanisms to explain the superior glucose control with an insulin pump compared with MDI, including improved subcutaneous absorption of insulin	Thank you for your feedback. It was not within the scope at this guideline update to consider different types of insulin administration in people with type 2 diabetes.

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					with the consistent low basal rate insulin infusion with a pump, compared to the large depot of injected insulin, resulting in higher and more stable blood insulin concentrations. The improved treatment satisfaction with CSII might also lead to a reduced treatment burden and improved adherence; a patient preference for insulin pump therapy over MDI, because of convenience, flexibility and ease of use, has been reported previously (Edelman et al,. 2010; Raskin et al., 2003). It is now clear that a subgroup of people with type 2 diabetes patients who have poorly glycaemic control with elevated HbA1c levels despite optimal treatment with MDI can achieve improved clinical outcomes when switched to insulin pump therapy. This approach is increasingly supported by the clinical community, with a recent review in Nature advocating the use of pump therapy in certain patients: "Many patients with uncontrolled T2DM and a poor quality of life who are treated with MDI would benefit from current-technology insulin pump therapy." (Pickup, 2014). We urge NICE to take these new and important RCT findings and the increasing experience of insulin pumps therapy in clinical practice in type 2 diabetes into account within the context of the Clinical Guideline, and include this treatment	

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					option as a consideration in the recommendations for blood glucose management of these patients. Specifically, we propose that an addition is made to the 'Recommendations' section: Recommendation #65 (p.23). Under this recommendation we propose that the following statement should be included: • *Consider continuous subcutaneous insulin infusion (insulin pump therapy) for people with type 2 diabetes who:* - *Do not reach target HbA1c levels despite optimisation of therapy with a multiple daily injection regimen (basal/bolus treatment), and,* - *Are willing and able to undertake the associated training and ongoing supervision necessary with insulin pump therapy.* **References** Berthe, E. et al. 2007. Effectiveness of intensive insulin therapy by multiple daily injections and continuous subcutaneous insulin infusion: a comparison study in type 2 diabetes with conventional insulin regimen failure. Horm. Metab. Res. 39, 224–229. Edelman, S. et al. 2010. Insulin pump therapy in	

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					patients with type 2 diabetes. Safely improved glycemic control using a simple insulin dosing regimen. Diabet. Technol. Therapeut. 12, 627–633. Leinung, M. et al. 2013. Use of insulin pump therapy in patients with type 2 diabetes after failure of multiple daily injections. Endocr. Pract. 19, 9–13. Parkner, T. et al. 2008. Insulin and glucose profiles during continuous subcutaneous insulin infusion compared with injection of a long-acting insulin in type 2 diabetes. Diabet. Med. 25, 585–591. Pickup, J. 2014. Insulin pump therapy for type 2 diabetes mellitus. Nat. Rev. Endocrinol. 10; pp. 647–649. Raskin, P. et al. 2003. Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in type 2 diabetes: a randomized, parallel-group, 24-week study. Diabetes Care 26, 2598–2603. Reznik, Y. et al. 2014. Insulin pump treatment compared with multiple daily insulin injections for the treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet; 384(9950):1265-72.	

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335	Medtronic Limited	NICE	27	3 (1.6.34)	We would like to reiterate the previous comment with regards to the NICE version of the Clinical Guideline. Again, we urge NICE to consider these new findings on the clinical effectiveness of continuous subcutaneous insulin infusion (insulin pump) therapy in a type 2 diabetes patient subgroup (Reznik et al., 2014) for inclusion in the NICE version of the Clinical Guideline. As outlined above, there is sufficient evidence for this therapy to be considered as a beneficial treatment option for a specific patient cohort within NICE recommendation 1.6: Insulin-based treatments – 1.6.34: "Initiate insulin therapy from a choice of a number of insulin types and regimens". Under this recommendation we propose that the following statement should be included: • *Consider continuous subcutaneous insulin infusion (insulin pump therapy) for people with type 2 diabetes who:* - *Do not reach target HbA1c levels despite optimisation of therapy with a multiple daily injection regimen (basal/bolus treatment), and,* - *Are willing and able to undertake the associated training and ongoing supervision necessary with insulin*	Thank you for your feedback. It was not within the scope at this guideline update to consider different type of insulin administration in people with type 2 diabetes.

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					pump therapy. Reznik, Y. et al. 2014. Insulin pump treatment compared with multiple daily insulin injections for the treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. Lancet; 384(9950):1265-72.	
333	Medtronic Limited	Full and NICE versions	General	General	Thank you for the opportunity to comment on this guideline update. We are concerned, however, that there is no mention in either the full guideline or NICE guideline of the role of continuous subcutaneous insulin infusion (CSII, insulin pump therapy) in the management of type 2 diabetes, and we would like to draw the attention of NICE to recent randomised controlled trial (RCT) and observational study evidence that has emerged for the safety and effectiveness of insulin pump therapy in sub-groups of people with type 2 diabetes. These recently published data would not have been included in the evidence review, therefore to ensure that the Clinical Guideline is contemporary on publication we recommend that NICE considers these study findings as described in our subsequent comments.	Thank you for your feedback. It was not within the scope at this guideline update to consider different type of insulin administration in people with type 2 diabetes.
595	Merck Serono	Full	12	Section 1.3.5 Drug treatment	The draft guidelines suggests a complete break from previous guidelines$_1$ in the approach dealing with patients not able to tolerate standard release metformin. It has been reported throughout the evidence review within the guidelines that metformin is	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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				lines 16-20	still the only type 2 diabetes medication that has established morbidity and mortality benefits. The removal of the metformin MR, means that patients intolerant of metformin due to gastrointestinal issues, have not been considered and will have no other option, but to move to alternative medications. This escalation of pharmacotherapy to more costly treatments may be avoided by offering a trial of modified-release metformin which has been shown to improve gastrointestinal tolerability compared to standard release metformin[1] and still offer the mortality and morbidity benefits of metformin as shown by the UKPDS studies. This change from previous NICE guidelines has the potential to overlook a key step within the treatment pathway and recommend premature escalation to more costly treatments. 1. Blonde L, Dailey G, Jabbour SA et al. Gastrointerstinal tolerability of extended-release metformin tablets compared to immediate-release	recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
596	Merck Serono	Full	166	Section 8.4.1 Line 24-25	Merck Serono agrees that a different mode of action of added medicines may add a complimentary effect to an existing drug treatment. However we believe that a different drug delivery mechanism may also improve the effectiveness of medication and that this should be included within guidelines. The different delivery mechanism of Metformin MR versus standard release, means that some	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release

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					patients may be effectively treated with metformin, without the need of progressing to another medication.	metformin is not tolerated.
597	Merck Serono	Full	192	Section 8.4.5, line 7 and 8	Metformin MR has been assessed in a U.K. Cost-Utility Analysis (CUA) which has not been captured within this review. In a resubmission to the Scottish Medicines Consortium, Merck Serono presented a CUA comparing metformin MR with sulphonylureas and pioglitazone in patients with type 2 diabetes mellitus who have stopped treatment with metformin IR due to side effects. The SMC concluded that: "*Despite some weaknesses, the economic case was considered demonstrated*"[1] Metformin MR was also not considered within the "original" economic analysis undertaken in the construction of these guidelines. Merck Serono is concerned that the economic benefits of Metformin MR have not been reported to the GDG and have been dismissed without consideration. 1. (SMC148/04).	Thank you for your feedback. The NICE Guidelines Manual (2012) states only published economic evaluations are considered for inclusion. Whilst modified-release metformin did not have the necessary evidence to be included in the health economic model, the guideline development group chose to recommend it as an alternative to standard-release metformin.
598	Merck Serono	Full	192	Section 8.4.6.2, line 33	As mentioned above metformin MR was not included within the Heath Economic assessment. One of the main reasons that patients are intolerant standard release metformin is due to Gastrointestinal (GI) side effects [1,2].	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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				and 34	Metformin MR was not considered as an alternative comparator to repaglinide, or other medications in this cohort. It should be understood that due to this exclusion, it can only be concluded from this evaluation that, for people who could not take "standard release" metformin, repaglinide was the most cost-effective option. However, this may not be the case for the group who require a change in their medication due to GI effects. 1. Levy J, Cobas RA, Gomes MB. Assessment of efficacy and tolerability of once-daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2010;2:1 2. Blonde L, Dailey G, Jabbour SA et al. Gastrointerstinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Current Medical Research & Opinion* 2006;20(4):565–572.	recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
599	Merck Serono	Full	196-197		Merck Serono welcomes the acknowledgment by the GDG that "*Drug intolerability (due to adverse effects) and change in body weight have a negative impact on overall diabetes management and on the individual's quality of life.*" We agree with this principle and believe that medications which can improve tolerability for patients should be included within guidelines and that this option should remain within the latest version.	Thank you for your feedback.
60	Merck	Full	198	Line	The GDG discussed that the gradual dosing and	Thank you for your feedback. The guideline

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0	Serono			38, Table 61: Trade-off between benefits and harms	titration may help reduces gastrointestinal adverse events acknowledging that it is an issue with standard release metformin. It should be noted that even with dose titration there are still patients who are intolerant to standard metformin due to GI side effects[1] The evidence, however "limited", demonstrates that modified release metformin does improve GI tolerability. Merck Serono would like to suggest that any conclusion on most appropriate method to treat patients intolerant of standard release metformin should be based on this evidence. 1. Levy J, Cobas RA, Gomes MB. Assessment of efficacy and tolerability of once-daily extended release metformin in patients with type 2 diabetes mellitus. Diabetol Metab Syndr 2010;2:1	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
601	Merck Serono	Full	199	Line 38, Table 61: Consideration of health benefits and reso	Merck Serono welcomes the GDGs acknowledgement on the long term benefits of metformin outside of the reduction of HbA1c. In this section the GDG did not consider the economic evidence supporting the use on metformin MR in preventing patients who are intolerant of standard release metformin, due to GI effects and the resulting progression to alternative medications. We would like to suggest that this evidence is considered by the GDG in this review and the reinstatement of metformin MR in line with previous NICE guidelines.	Thank you for your feedback. Whilst modified-release metformin did not have the necessary evidence to be included in the health economic model, the guideline development group chose to recommend it as an alternative to standard-release metformin.

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594	Merck Serono	Full	General		Merck Serono welcomes the review of the NICE clinical guidelines in type 2 Diabetes. As the incidence of this disease increases at an unprecedented scale, the number of therapies available are also increasing to meet this need. Updating of the present guidelines is necessary to support the implementation evidence based medicine in this area. However Merck Serono is concerned that Metformin Modified Released (MR) has been overlooked, or without full consideration of the evidence, has been removed from the present version of these guidelines.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
737	Merck Sharp and Dohme Ltd	NICE Full	1.6.27 Page 15	2	**<u>Metformin + pioglitazone + sitagliptin</u>** MSD believes that the GDG have made an error during the second intensification treatment algorithm. Patients who have not been successfully managed on metformin + pioglitazone and who are contraindicated to a sulfonylurea should be offered a DPP-4i as per licenced indication (see comment 5, table 1) before progressing to insulin. This offers patients and clinicians another choice, and delays the use of insulin. MSD would like to understand how the GDG developed the list intervention combinations reported in Table 29, page 51 of appendix F as	Thank you for your feedback and highlighting that the Fonseca 2013 paper is missing from our excluded list of studies. This paper was identified in our searches, and excluded at the title/abstract stage as it was clearly outside the scope of the review because it compared across treatment strategies, that is, metformin+pioglitazone+sitagliptin (3 oral combination) versus metformin+pioglitazone+placebo (2 oral combination). The excluded list of studies only contains citations of retrieved full text papers. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available

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					we have two significant concerns: • firstly, the GDG has failed to identify the licenced combination of metformin + pioglitazone + sitagliptin, as listed in the SPC of sitagliptin[1]. As a result they have failed to consider the clinical and cost-effectiveness of this option, resulting in the lack of a recommendation for this triple therapy combination • Secondly, the GDG also included an off label combination of metformin + repaglinide + sulfonylurea; this should be removed. This does not follow the recommendations of NICE, GMC, and the MHRA (see comment 5) As the manufacturer of sitagliptin we are concerned that the triple therapy combination of metformin + pioglitazone + sitagliptin has not been reviewed as part of the guideline looking at the clinical effectiveness or the cost-effectiveness of this combination, despite being a licenced and a particularly relevant option for patients given the positioning of pioglitazone in the guideline. The Fonseca et al. 2013[2] study as described below was not listed in appendix L (excluded publications). Therefore, MSD have reservations around the robustness/ implementation of the search strategy used by the GDG, and question what other data may not have been identified.	licensed combinations. The treatment options listed in appendix F table 29 are those for whom clinical evidence was found, in line with the evidence selection criteria detailed in the full guideline (see sections 8.4.2 and 8.4.12).

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					• Fonseca et al. 2013[2], reported a statistically significant reduction in HbA1c at 26 weeks for patients treated with sitagliptin in combination with pioglitazone and metformin vs. placebo ($p<0.001$). The addition of sitagliptin to metformin and pioglitazone was generally well tolerated[2]. It is of critical importance to patient care that the GDG adds the triple combination of metformin + pioglitazone + sitagliptin to the review for second intensification, and fully evaluate the clinical and cost-effectiveness of this combination. This is an important triple therapy option that is relevant to patients with type 2 diabetes mellitus – and we are extremely concerned that this appears to have been missed in the assimilation of evidence, even though it is a licensed option and fits the remit of the scope of this guideline. **Reference** 1. Januvia 25mg, 50mg, 100mg film-coated tablets. Summary of product characteristics. EMC, November 2014; http://www.medicines.org.uk/emc/medicine/19609/SPC/; accessed 18 February 2015 2. Fonseca, V et al. "Efficacy and safety of sitagliptin added to ongoing metformin	

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					and pioglitazone combination therapy in a randomized, placebo-controlled, 26-week trial in patients with type 2 diabetes" Journal of Diabetes and Its Complications 27 (2013) 177–183	
738	Merck Sharp and Dohme Ltd	Full Guidance	174		**<u>Health economic analyses</u>** MSD believes that the health economic analyses and the decisions made by the GDG do not fully reflect the safety data available for the technologies assessed. In the health economic modelling, the only adverse events that were modelled are hypoglycaemia, nausea and dropouts due to intolerance. There are, however, safety concerns regarding a number of drugs that have been evaluated in the guideline. For example, pioglitazone is associated with a raised risk of fractures and this needs to be fully incorporated into the health economic modelling – especially when the cost-utility analyses are the primary tool used by the GDG to make recommendations. Furthermore, there is extensive RCT data on the cardiovascular risk associated with sulfonylureas – and given that the primary aim of treating patients with blood glucose lowering drugs is to lower the risk of micro and macrovascular complications, the health economic modelling should be adapted to reflect the results from this meta-analysis and	Thank you for your feedback. Long-term risks associated with different treatment options were assessed in a separate review question (see section 8.5). Whilst it was not possible to incorporate these risks within the health economic modelling, it is of note that no type 2 diabetes health economic models currently incorporate the long-term risks associated with different treatment options. The guideline development group considered long-term risk evidence alongside clinical and cost effectiveness and noted the need to consider MHRA safety advice when discussing the risks and benefits of treatment options with people with type 2 diabetes.

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					assess the impact on the cost-utility results. • In a 2013 systematic review and meta-analysis of randomised clinical trials, sulfonylureas versus other oral anti-hyperglycaemic agents were associated with a significant increase in mortality (OR: 1.22 [1.01;1.49]) and stroke (OR: 1.28 [1.03;1.60])[1]. • Sulfonylureas were associated with a significant increase in risk of stroke when compared to DPP-4's (OR: 4.51 [1.65;10.79])[1]. • Two CV safety trials have been performed with DPP-4i's, in which both demonstrated that there is no increased CV risk from adding the DPP-4i to standard of care vs standard of care[2,3]. **Reference** 1. Monami, M et al. "Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials". *DOM*, 15: (2013) 938-953. 2. Scirica B, et al. "Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus" *N Engl J Med* (2013)DOI: 10.1056 3. White W, et al. "Alogliptin after acute coronary syndrome in patients with type 2 diabetes" *N Engl J Med* (2013)DOI: 10.1056	

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722	Merck Sharp and Dohme Ltd	NICE	General		**<u>Burden of Type 2 Diabetes Mellitus</u>** MSD welcome the update of NICE Clinical Guideline 87 (CG87) 'The clinical guideline for type 2 diabetes in adults, to support the needs of patient and clinician in the management of type 2 diabetes (T2DM). The latest National Diabetes Audit (NDA)[1], conducted between 2012 and 2013, identified over 2.2 million patients in England and Wales. The prevalence of T2DM is considerable, and is exacerbated by numerous comorbidities; namely cardiovascular disease, and chronic kidney disease. The NDA commented '*The incidence and prevalence of Type 2 diabetes continues to increase at an alarming rate in England and Wales, increasing the disease, and diabetes complication burden on the NHS as a whole…*'[1]. Given the size (and growth) of the patient population with T2DM, coupled with the complexity of the disease, patient and clinician choice is critical. Diabetes UK (2012) has quantified the cost of T2DM on the NHS at ~£12 billion per year[2]. Of this, approximately 68% is incurred in the inpatient setting[2]. The overall cost of diabetes drugs has been estimated by Diabetes UK to account for ~6% of the total costs of T2DM care (~£12 bn.)[2]. This breakdown of cost illustrates	Thank you for your feedback.

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					both the disproportionate use of NHS funding for inpatient care; and a false economy driven by the use of lowest acquisition cost medications, which this current draft guideline still does not address. MSD strongly believes that clinicians need access to a wide range of anti-hyperglycaemic agents that are safe and clinically efficacious to effectively manage the growing number of patients with T2DM and minimise the long-term complications associated with the disease. **Reference** 1. Health and Social Care Information Centre, National Diabetes Audit 2012-2013 Report 2: Complications and Mortality. January 2015. PDF online, http://www.hscic.gov.uk/catalogue/PUB16496/nati-diab-audi-12-13-rep2.pdf; accessed 18 February 2015 2. Diabetes UK, cost of diabetes treatment in the UK. Diabetes UK, (source: Source: Kanavos, van den Aardweg and Schurer: Diabetes expenditure, burden of disease and management in 5 EU countries, LSE (Jan 2012)); accessed 18 February 2015	
723	Merck Sharp and Dohme	NICE	General		**Individualised patient care in Type 2 Diabetes**	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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	Ltd		1.1		MSD commends the recommendation to adopt an individualised approach to diabetes care, focusing on 'the person's needs and circumstances, taking into account their personal preferences, comorbidities, risk of polypharmacy, and their ability to benefit from long-term interventions due to reduced life expectancy'. This recommendation is in line with both the UK medical optimisation strategy[1], NHS five year forward plan[2] and the international American Diabetes Association (ADA)-European Association for the Study of Diabetes (EASD) position statement on the management of hyperglycaemia in T2DM[3]. However, the individualised patient approach recommended in section 1.1 of the NICE guideline is not consistently applied through the recommendations. MSD are deeply concerned that recommendations for pharmacological therapies are heavily reliant on cost containment. This approach contradicts three of the five guiding principles (principle: 1, 3 and 4) of the medical optimisation strategy[1] and is counter-intuitive of the NICE five year forward plan that states the UK want to adopt a 'national evidence-based diabetes prevention programme modelled on proven UK and international models'[2]. MSD believe that cost containment has been	pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					favoured at the expense of patient safety and patient/ clinician choice. For example, patient/ clinician choice has been sacrificed at second intensification where the guideline development group (GDG) have failed to identify all licenced treatment options for sitagliptin (discussed in comment 5, Table 1). The implications of using a cost-centric approach are: • Limited treatment choice • Disregard for patient safety • Lack of flexibility within the proposed guideline • Disassociation from individualised patient care • Short sighted savings (false economy) that will ultimately add greater financial burden on the NHS through: adverse events, hypoglycaemic episodes requiring hospitalisation, and long-term microvascular and microvascular complications. A critical analysis of the draft NICE guideline highlighted concern for patient care and safety; the authors believe that if the proposed guideline is enacted it 'will set back modern diabetes management by decades'[4]**.** MSD hold the same opinion, and do not believe that the three years taken to develop this draft guideline	

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					are aligned with the usual high quality evidence-based recommendations developed by NICE. In the interest of patient safety and individualised care, MSD insist that clearly defined populations are reported for each intervention (as per licenced indication and evidence considered within the cost-utility analyses), which includes health warnings and contraindications as specified by the European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) at all stages of treatment therapy. This would make the whole guideline truly patient centric, giving both patient and clinician choice and ensuring appropriate implementation of the recommendations in the NHS **Reference** 1. Royal Pharmaceutical Society, Medicines Optimisation: Helping patients to make the most of medicines, May 2013. PDF online, http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf; accessed 18 February 2015 2. NHS Five Year Forward View, October 2014. PDF online, http://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf;	

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					accessed 18 February 2015 3. American Diabetes Association (ADA), Standards of Medical Care in Diabetes 2015. January 2015. PDF online. http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/Documents/January%20Supplement%20Combined_Final.pdf; accessed 18 February 2015 4. O'Hare, J et al. "The new NICE guidelines for type 2 diabetes- a critical analysis" Editorial, Available online. Br J Diabetes Vasc Dis 2015;15:xx-xx http://dx.doi.org/10.15277/bjdvd.2015.006; Accessed 18 February 2015	
724	Merck Sharp and Dohme Ltd	NICE	General		**Implementation** MSD believes that the NHS will face numerous challenges when trying to implement the proposed clinical guideline (CG87). The "one size fits all" analogy that this guideline appears to have followed is not in the best interest of 2.2 million patients with T2DM, nor does it promote flexibility for health care professionals. The critical analysis by O'Hare considered this draft guideline to be unworkable[1]. MSD commissioned a survey of GPs (n=101) to understand their knowledge of individualised patient care, and to further assess their confidence when prescribing oral antidiabetic	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual

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					agents, namely repaglinide and/ or pioglitazone in patients with T2DM[2]. The results show that 90% of GPs surveyed believe that an individualised patient approach should be adopted[2]. However, numerous barriers that prevent the implementation of an 'individualised patient approach' were identified, including; a lack of consultation time (68%), a requirement of specialised expertise for complex patients (45%), and budget constraints (50%), were highlighted[2]. GPs noted that patients with co-morbidities were either somewhat likely or very likely to benefit from an individualised patient approach, namely patients with heart failure, BMI ≥35, increased risk of fractures, and hypoglycaemia etc[2]. MSD are concerned that the barriers to implementation, listed above, would predominantly affect T2DM patients already complicated by high risk comorbidities. If this guideline remains unchanged it will generate local inequality as CCGs will struggle to adapt these confusing guidelines into a workable framework. We have received ad-hoc feedback that CGGs may need to develop their own local guidelines, for drug treatments, to control blood glucose due to limitations of the current draft guideline. This would result in a huge duplication of work in	clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					the NHS, at a time when driving efficiencies is key; this would also be a considerable failure for both patients and the NHS. **Reference** 1. O'Hare, J et al. "The new NICE guidelines for type 2 diabetes- a critical analysis" Editorial, Available online. Br J Diabetes Vasc Dis 2015;15:xx-xx 2. MSD. Data on file. GP survey, clinical practice in type 2 diabetes patients February 2015	
726	Merck Sharp and Dohme Ltd	NICE FULL	General		**Off-label use of oral anti-diabetic drugs (OAD)** The update to NICE CG87, the Clinical Guideline for type 2 diabetes in adults, followed the process and methods guide "The Guidelines Manual 30 November 2012"[1]. MSD have identified a number of concerning deviations in the development of the T2DM guideline that need to be addressed. DPP-4i's have been treated as a class, with no differentiation. All DPP-4i's have different licence indication(s); therefore it is inappropriate that recommendations are attributed to the class as a whole. MSD consider the use of DPP-4i's off-licence to be unacceptable, and the decision to	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are

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					recommend the DPP-4i as a class to be irrational. There is no need for a DPP-4i to be used off-label, as there is at least one DPP-4i that is licensed for each intensification step and in each relevant combination (please see licenced indications in table 1). NICE should state which DPP-4i's have been assessed at each treatment intensification stage and list the interventions considered in the de-novo cost utility analysis. If a DPP-4i is recommended where no evidence has been reviewed or does not have a label for that indication, this should be clearly documented in the NICE version of the guideline as per the guidelines manual. MSD believe that the GDG have deviated from process, when recommending a DPP-4i. The GDG have not reviewed all DPP4-i's and have not considered the differences in licenced indication(s). MSD would ask the GDG to refer to the recommendations of the MHRA, General Medical Council (GMC), and the NICE guidelines manual (2012) regarding the use of prescription medicine for off-label use. The recommendations of these bodies are summarised below. The NICE guidelines manual states strict guidance for recommending outside a drug's	appropriate, choose the option with the lowest acquisition cost).

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					indication (9.3.6.3, pages 152-153 of The Guidelines Manual 30 November 2012)[1]: • "Off-label use may be recommended if the clinical need **cannot** be met by a licenced product and there is a sufficient evidence base and/or experience of using the drug to demonstrate its safety and efficacy to support this." This is not the case, please see Table 1. The MHRA[2] ask that health care professionals: • be satisfied that an alternative, licenced medicine would **not meet the patient's needs** before prescribing an un-licenced medicine • be satisfied that such use would better serve the patient's needs than an appropriately licenced alternative before prescribing a medicine off-label • be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy • take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up The General Medical Council (GMC 2013)[3] in paragraph 69 of the Good practice in prescribing and managing medicines and devices states	

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					that medication should only be used within its licenced indication unless: • following assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient. • there is no suitably licensed medicine that will meet the patient's need i.e. there is no licensed medicine applicable to the particular patient. • a medicine licensed to treat a condition or symptom in children would nonetheless not meet the specific assessed needs of the particular child patient, but a medicine licensed for the same condition or symptom in adults would do so • the dosage specified for a licensed medicine would not meet the patient's need • the patient needs a medicine in a formulation that is not specified in an applicable licence • a suitably licensed medicine that would meet the patient's need is not available. This may arise where, for example, there is a temporary shortage in supply. **Table 1,** DPP-4i licenced indications[4-8]	

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Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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Intensification	Licenced indications	alogliptin ▶	linagliptin ▶	saxagliptin	sitagliptin	vildagliptin
Monotherapy	If metformin is contraindicated or not tolerated	☒	✓	✓	✓	✓
1st intensification	Add-on to metformin	✓	✓	✓	✓	✓
	Add on to SU	✓	☒	✓	✓	✓
	Add on to TZD	✓	☒	✓	✓	✓
2nd Intensification	Add on to metformin + SU	*	✓	✓	✓	✓
	Add-on to metformin + TZD	✓	☒	☒	✓	☒
Insulin	Add on to insulin +/- metformin	✓	✓	✓	✓	✓

* The safety and efficacy of alogliptin when used as triple therapy with metformin and a sulfonylurea have not been fully established[5].

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					Reference 1. NICE, Process and methods guides, The guidelines manual. November 2012. http://www.nice.org.uk/article/pmg6/resources/non-guidance-the-guidelines-manual-pdf; accessed 18 February 2015 2. MHRA, Drug Safety Update, Off-label or unlicensed use of medicines: prescribers' responsibilities, April 2009. https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities#in-practice; accessed 18 February 2015 3. General medical Council UK (GMC), New guidance on Good practice in prescribing and managing medicines and devices, January 2013. http://www.gmc-uk.org/Good_practice_in_prescribing.pdf_58834768.pdf; accessed 18 February 2015 4. Januvia 25mg, 50mg, 100mg film-coated tablets. Summary of product characteristics. EMC, November 2014; http://www.medicines.org.uk/emc/medicine/19609/SPC/; accessed 18 February 2015 5. Vipdidia 6.25mg, 12.5mg, 25mg film-	

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					coated tablets. Summary of product characteristics. EMC, January 2015; http://www.medicines.org.uk/emc/medicine/28513; accessed 18 February 2015 6. Trajenta 5 mg film-coated tablets. Summary of product characteristics. EMC, October 2014; http://www.medicines.org.uk/emc/medicine/25000; accessed 18 February 2015 7. Onglyza 2.5mg & 5mg film-coated tablets. Summary of product characteristics. EMC, October 2014; http://www.medicines.org.uk/emc/medicine/22315; accessed 18 February 2015 8. Galvus 50 mg Tablets. Summary of product characteristics. EMC, December 2014; http://www.medicines.org.uk/emc/medicine/20734; accessed 18 February 2015	
727	Merck Sharp and Dohme Ltd	NICE FULL	General		**DPP-4i product differentiation with a focus of individualised patient care** MSD has serious concerns about the process in which the GDG has arrived at the recommendation for the DPP-4i's with respect to the statement "if a DPP-4i is preferred, choose the option with the lowest acquisition cost" (sections 1.6.21, 1.6.22, 1.6.23, 1.6.24,1.6.26 and 1.6.27 in NICE version). MSD consider this to be unfair based on the evidence presented within this pro-forma, and would reserve the	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a

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					right to further challenge this statement if retained in the final guideline. MSD have presented separate evidence statements relating to licenced indication (comment 5, table 1), and use in patients with renal and hepatic impairment that support this statement (See comment 7, Table 1 and 2). There are four different types of economic evaluation. The standard approach adopted by NICE for assessing the cost-effectiveness of technologies in clinical guidelines and technology appraisals is specifically using cost-utility analysis (see section 5.1.11, Guide to the methods of technology appraisal 2013)[1]. There are a number of other types of economic evaluation, such as cost-minimisation. None of these are accepted by NICE according to the process guide. One of the major limitations of cost-minimisation is that it is only appropriate where the intervention of interest has been demonstrated to be equivalent to all relevant comparators for all domains of efficacy and safety. For the GDG to have arrived at making a recommendation to use 'the DPP-4i with the lowest acquisition cost', the GDG appear to have inadvertently used a cost-minimisation approach, which is not appropriate based on	generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					NICE processes and the clinical data available. The recommendations presented within the full guidance document should be based on the de novo cost-utility analyses conducted (as specified by the NICE reference case), which do not support this lowest acquisition cost statement for the DPP-4i class. Further to this: • The work supporting the development of this guideline has not demonstrated that all of the DPP-4i's are equivalent in their efficacy and safety either through head-to-head randomised clinical trials or network meta-analysis – and therefore adopting a cost minimisation approach is not appropriate. • MSD are not aware of any equivalence randomised clinical trials between DPP-4i molecules. • One head-to-head randomised clinical trial showed non-inferiority for saxagliptin vs. sitagliptin when HbA1c (primary endpoint) and fasting plasma glucose (FPG) were considered. However, sitagliptin was numerically superior in the primary outcome for HbA1c reduction and demonstrated statistically significant improvement in FPG vs. saxagliptin. o The results of this 18 week phase III RCT (N=801) showed adjusted mean changes in	

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					HbA1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were −0.52 and −0.62%, respectively[2]. The between-group difference was 0.09% (95% confidence interval, −0.01 to 0.20%), which while non-inferior, demonstrated a numerical advantage for sitagliptin[1]. FPG was assessed at 18 weeks, also. The results show that the addition of saxagliptin and sitagliptin produced adjusted mean changes in FPG of −0.60 mmol/L (−10.8 mg/dL) and −0.90 mmol/L (−16.2 mg/dL), respectively. This was statistically significant and favoured sitagliptin; mean difference 0.30 mmol/L (5.42 mg/dL); 95% CI, 0.08–0.53 mmol/L (1.37–9.47 mg/dL)[2]. • MSD would like to draw the GDGs attention to additional evidence that that further supports the differentiation of DPP-4i molecules: o Tatosian et al. 2013 examined patients (n=22) treated with either 5mg saxagliptin q.d,	

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					100mg sitagliptin q.d, 50mg vildagliptin q.d, 50mg vildagliptin b.i.d., or placebo for 5 days in a randomised five period cross over study[3]. The primary endpoint measured trough levels (%) of DPP-4i inhibition. The least-squares mean trough value (% DPP-4 inhibition) was 73.5% (saxagliptin 5mg q.d.), 91.7% (sitagliptin 100mg q.d.), 28.9% (vildagliptin 50mg q.d.), 90.6% (vildagliptin 50mg b.i.d.), and 3.5% (placebo)[3]. The between group comparisons favoured sitagliptin and was statistically significant vs. saxagliptin 5mg (18.2%, p<0.001), vs. vildagliptin 50mg q.d. (62.9%, p<0.001), vs. placebo (87.8%, p<0.001) and was numerically favourable vs. vildagliptin 50mg b.i.d (1.1%, p-0.128)[3]. ○ The German HTA body (GBA) considered the assessment of DPP-4i's appraised by the Institute for Quality and Efficiency in Health Care (IQWIG). Sitagliptin and saxagliptin were shown to	

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					provide added benefit for the outcome 'reduced hypoglycaemia' when compared to a sulfonylurea. In addition sitagliptin was shown to provide added benefit when used in combination with metformin vs. metformin and a sulfonylurea. The GBA did not find added value for remaining DPP-4i's[4]. • MSD cannot agree with the assumption made by the GDG for initial drug therapy which is presented on page 197, table 61, of the full guidance document. The GDG state that '…linagliptin and saxagliptin would be expected to perform well if data were available for inclusion in these analyses…' – as stated, no data for these interventions was available for the cost-utility analyses. The cost effectiveness data reported for DPP-4i's related only to two DPP-4i's, sitagliptin and vildagliptin – of which, sitagliptin was considered to be the most cost effective in people who could not take metformin, repaglinide or pioglitazone (CG87 Full guidance, Section 8.4.6.2, page 196). • MSD disagrees with the assumption made by the GDG for first	

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					intensification, reported in table 74 (CG87 Full Guidance, page 222-223) of the full guidance document. This assumes a class effect for the DPP-4i's when not all DPP-4i's have been considered within the cost-utility analyses. The cost-utility data reported for DPP-4i's related to sitagliptin, linagliptin, and vildaglitpin only. The GDG also acknowledged that data for DPP-4i's was sporadic according to treatment intensification level, and that the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. The GDG did not want to confuse the reader by alternating between the DPP-4i class and individual agents throughout the guideline, and for this reason decided to consistently refer to DPP-4i's as a class. MSD consider this statement and approach inappropriate. • MSD fail to understand how the GDG decided to use the statement "choose the lowest acquisition cost DPP-4i", at second intensification when the only DPP-4i considered in the cost-utility analysis was sitagliptin. The cost-utility analysis did not evaluate linagliptin, saxagliptin, or vildagliptin; therefore, the	

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					final guidance document should only recommend sitagliptin for use in combination with metformin and sulfonylurea. The GDG also failed to identify all licenced combinations for sitagliptin at second intensification (comment 5, table 1). NICE have not provided evidence to support clinical equivalence and have irrationally applied a cost minimisation analysis to reach the recommendation on the DPP-4i's. MSD requests that in the NICE version of the guideline, the approach using cost-utility analyses to make recommendations is used and it is stated, with two key changes to the NICE version: • The GDG should not recommend a DPP-4i where no evidence has been considered; and should state which DPP-4i's were fully assessed (i.e. both clinical effectiveness and cost-effectiveness evaluated). For example, there is only cost-utility results for first intensification presented for linagliptin, sitagliptin, and vildagliptin for first intensification (see section 8.4.9.2, Full version). This is consistent with the approach taken in the current NICE Clinical Guideline for Type 2 Diabetes that was published in 2009[5], where the	

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					DPP-4i's that were assessed in that guideline was stated, e.g. DPP-4 inhibitors (sitagliptin, vildagliptin) (see section 1.6.1). As a cost minimisation approach is not appropriate and there is no evidence that all DPP4-i are equivalent, MSD insist that the lowest acquisition cost statement for DPP-4i's is removed. **Reference** 1. NICE, Guide to the methods of (TA) 2013, April 2014, http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf; accessed 18 February 2015 2. Scheen, A et al. "Efficacy and safety of saxagliptin in combination with metformin compared with sitagliptin in combination with metformin in adult patients with type 2 diabetes mellitus" Diabetes Metab Res Rev 26: (2010) 540–549 3. Tatosian, D et al. "Dipeptidyl Peptidase-4 Inhibition in Patients with Type 2 Diabetes Treated with Saxagliptin, Sitagliptin, or Vildagliptin" Diabetes Ther. (2013) 4. IQWIG, First assessment of the	

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					established drug market: advantage for sitagliptin, https://www.iqwig.de/en/press/press-releases/press-releases/first; accessed 27 February 2015 5. NICE CG87, Type 2 diabetes: The management of type 2 diabetes. May 2009. https://www.nice.org.uk/guidance/cg87; accessed 18 February 2015	
728	Merck Sharp and Dohme Ltd	NICE Full	General		**Considerations for the DPP-4i use in renal/ hepatic impairment** MSD ask that in the final NICE guidance document interventions should be listed according to their licenced indication and should reflect appropriate use, i.e. appropriate use in patients with renal and/or hepatic impairment (table 1 and 2). Due to the multi-faceted nature of T2DM in addition to the DPP-4i licence variation, the GDG should provide added clarity within the final guidance document for these drugs. These data would also suggest that it is inappropriate to consider the DPP-4i's simply as a class. To highlight the complexity of DPP-4i prescribing clinicians need to not only consider the licensed indications for each DPP-4i (comment 5, table 1) but also the renal and hepatic tolerability of patients summarised in	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the

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					table 1 and 2 below. It is estimated that 1/3 of patients with T2DM will develop renal impairment; this is ~700,000 patients in the UK. As you will note, there are differences in terms of SPC recommendations and cautions, for example: • Saxagliptin is not recommended for end-stage renal disease. Further complexity is added for people with T2DM and renal impairment, in that both licensed indications need to be considered with any renal restrictions. • Linagliptin does not hold a licence for first intensification add-on to sulfonylurea or thiazolidinedione, or at second intensification add on to metformin and thiazolidinedione [2]. In the case of saxagliptin, this is suitable in patients with mild and moderate renal impairment, but does not hold a licence for second intensification when added to metformin and thiazolidinedione. This is further complicated by the fact it is not recommended (SPC contraindicated) in patients with severe hepatic impairment[4] MSD commends the level of prescribing detail for patients with varied levels of renal function during initial drug therapy with metformin. This supports the individualised patient approach taken to T2DM care. A similar approach should	guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

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be taken with the DPP-4i's.

<u>Table 1.</u> DPP-4 use in patients with renal impairment[1-5]
<table>
<tr><th>Degree of renal impairment</th><th>alogliptin ►</th><th>linagliptin ►</th><th>saxagliptin</th><th>sitagliptin</th></tr>
<tr><td colspan="5">Mild</td></tr>
<tr><td>CrCl ≥50ml/min</td><td>25mg</td><td>5mg</td><td>5mg</td><td>100mg</td></tr>
<tr><td colspan="5">Moderate</td></tr>
<tr><td>CrCl ≥30 to <50ml/min</td><td>12.5mg</td><td>5mg</td><td>2.5mg</td><td>50mg</td></tr>
<tr><td colspan="5">Severe</td></tr>
<tr><td>CrCl <30ml/min</td><td>6.25mg W/C</td><td>5mg</td><td>2.5mg W/C</td><td>25mg</td></tr>
<tr><td colspan="5">ESRD</td></tr>
<tr><td><15ml/min</td><td>6.25mg W/C</td><td>5mg</td><td>N/R</td><td>25mg</td></tr>
</table>
BD= bi-daily; N/R = not recommended; OD = once daily;
W/C= use with caution

<u>Table 2.</u> DPP-4 use in patients with hepatic
</td><td></td></tr>
</table>

<table>
<tr><th>ID</th><th>Stakeholder</th><th>Document</th><th>Page No</th><th>Line No</th><th>Comments
Please insert each new comment in a new row</th><th>Developer's response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>impairment[1-5]
<table>
<tr><th>Degree of hepatic impairment*</th><th>Mild</th><th>Moderate</th><th>Sev</th></tr>
<tr><td>alogliptin</td><td>25mg</td><td>25mg</td><td>N/R</td></tr>
<tr><td>linagliptin</td><td colspan="3">5mg/ PK/ No dose adjustment required/ Clinical experience lack</td></tr>
<tr><td>saxagliptin</td><td>5mg</td><td>5mg with caution</td><td>NR</td></tr>
<tr><td>sitagliptin</td><td>100mg</td><td>100mg</td><td>100m No cli exper</td></tr>
<tr><td>vildagliptin</td><td colspan="3">N/R/ Including Patients with pre-treatment ALT or AST >3 x ULN</td></tr>
</table>
N/R, not recommended
*Child-Pugh Scores 6-12

<u>Reference</u>

1. Januvia 25mg, 50mg, 100mg film-coated tablets. Summary of product characteristics. EMC, November 2014; http://www.medicines.org.uk/emc/medicine/19609/SPC/; accessed 18 February 2015
2. Vipdidia 6.25mg, 12.5mg, 25mg film-coated tablets. Summary of product characteristics. EMC, January 2015; http://www.medicines.org.uk/emc/medicine/28513; accessed 18 February 2015
3. Trajenta 5 mg film-coated tablets.

</td><td></td></tr>
</table>

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					Summary of product characteristics. EMC, October 2014; http://www.medicines.org.uk/emc/medicine/25000; accessed 18 February 2015 4. Onglyza 2.5mg & 5mg film-coated tablets. Summary of product characteristics. EMC, October 2014; http://www.medicines.org.uk/emc/medicine/22315; accessed 18 February 2015 5. Galvus 50 mg Tablets. Summary of product characteristics. EMC, December 2014; http://www.medicines.org.uk/emc/medicine/20734; accessed 18 February 2015	
739	Merck Sharp and Dohme Ltd	NICE	General		**The use of glinides and Sulfonylureas when driving** MSD ask that the GDG carefully consider and amend the NICE clinical guideline to reflect the DVLA document INF188/2 (March 2013)[1]. This states that drivers with T2DM who manage their condition with either sulfonylurea or glinides must comply with the following statements: Group 1 drivers (car, motorcycle): • Must not have had more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months • Drivers must be under regular medical review	Thank you for your feedback. Recommendation 1.6.12 (NICE version) states "*Take the Driver and Vehicle Licensing Agency (DVLA) At a glance guide to the current medical standards of fitness to drive into account when offering self-monitoring of blood glucose levels for adults with type 2 diabetes.*" In addition, recommendation 1.6.13 (NICE version) notes that self-monitoring of blood glucose should be undertaken for adults with type 2 diabetes who are "*on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery*"**.** **The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of**

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					• Testing is dependent on clinical factors and driving frequency. <u>Group 2 vocational drivers (bus, lorries)</u> • No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12 months • Has full awareness of hypoglycaemia • Regularly monitors blood glucose at least twice daily and at times relevant to driving • Must demonstrate an understanding of the risks of hypoglycaemia • There are no other debarring complications of diabetes such as a visual field defect. These warnings, issued by the DVLA, raise doubt for the wide scale implementation of repaglinide in patients who are intolerant or contraindicated for metformin. • MSD recently completed a survey in ~1,500 drivers with T2DM treated with either oral sulfonylureas or glinides based therapies (ISGs), non-ISGs, diet alone, and or insulin alone. Hypoglycaemic events were common among patients treated with ISGs, experiencing either a severe or minor hypo in the past 12 months[2]. Drivers expressed concern about the impact of	**hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.**.

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					diabetes and driving[3]. Vocational drivers are also burdened by multiple testing (at least twice a day). **Reference** 1. DVLA, DVLA's current medical guidelines for professionals – conditions D to F. November 2014. https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals-conditions-d-to-f ; accessed 18 February 2015 2. Evans, M. et al. "Experience of hypoglycaemia in drivers with type 2 diabetes: results of an online survey". Diabetes UK poster abstract, March 2015 3. Feher, M et al. "Vocational driving, diabetes management and driving guidelines in people with type 2 diabetes" Diabetes UK poster abstract, March 2015	
741	Merck Sharp and Dohme Ltd	NICE	General		**TECOS CV safety study** MSD would like to inform the GDG that the cardiovascular safety study for sitagliptin (TECOS) is expected to be made public Q2 2015. TECOS, an event-driven trial, will report on approximately 14,724 patients with a median follow up expected to be ~3 years[1]. We will be submitting these data to the group for	Thank you for your feedback. Long-term drug safety was considered in a separate review question, with a search date cut off of June 2014. Any studies published after this date could not be included in this update.

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					consideration as soon as it is available. **Reference** 1. Bethel MA, et al. Regional, age and sex differences in baseline characteristics of patients enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS). Diabetes Obes Metab. 2015 Jan 20. doi: 10.1111/dom.12441. [Epub ahead of print]	
725	Merck Sharp and Dohme Ltd	NICE	General	1.6	**Testing and targets** MSD commends the individualised approach taken to HbA1c targets, as fundamentally described in CG87 (2009)[1]. MSD believe that regular testing (3-6 months initially followed by 6 monthly intervals) is useful and should remain. MSD welcome the introduction of individualised patient targets, namely in patient groups: • who are unlikely to achieve longer-term risk-reduction benefits (for example, people with a reduced life expectancy) • for whom tight glycaemic control poses risks • with a high risk of the consequences of hypoglycaemia (for example, people who are at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or	Thank you for your feedback.

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					operate machinery as part of their job (see comment 17) • for whom intensive management would not be appropriate (for example, people taking multiple drugs and people with significant comorbidities) These statements recognise the complexity of T2DM and the numerous patients groups who would benefit from tailored therapy. Although MSD cannot comment on the education or diet and lifestyle sections of this guideline, MSD recognises and fully supports the importance of patient education and diet management. MSD believe this is an integral part of managing patients with T2DM. **Reference** 1. NICE CG87, Type 2 diabetes: The management of type 2 diabetes. May 2009. https://www.nice.org.uk/guidance/cg87; accessed 18 February 2015	
734	Merck Sharp and Dohme Ltd	NICE	General	1.6.16	**Initial drug treatment** To improve both patient and clinician choice MSD ask that the GDG recommend the following at first intensification: *"If standard-release metformin is contraindicated or not tolerated consider initial drug treatment with*	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At

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					either: • *Pioglitazone (as per licensed indication)* ***or*** • *a DPP-4i (as per licenced indication*, and DPP-4i reviewed)* ***or*** • *a sulfonylurea"* *As per licenced indication as discussed in comment 5 in table 1**.** To maintain the focus of individualised patient care renal function should also be assessed (comment 7, table 1). This would give increased flexibility for clinician prescribing and take into consideration factors such as; comorbidities, interaction of polypharmacy, and patient lifestyle. A similar approach has been recommended by the ADA standards of medical care in diabetes 2015[1]. These guidelines state that patients who are intolerant or contraindicated to metformin should consider an initial drug from another drug class listed at first intensification (dual therapy). The options include either a: sulfonylurea, thiazolidinedione, DPP-4i, SGLT-2, GLP-1, and or basal insulin[1]. The evidence considered at initial therapy within the DPP-4i class was limited to sitagliptin and vildagliptin. Therefore, when recommending a DPP-4i at this treatment level only sitagliptin and vildagliptin should be listed.	first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. At initial therapy, the guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular

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					Warnings from the MHRA or EMA should be clearly documented. Therapies should be recommended according to their licence indication(s), and any recommendations outside of these approved licences are explicitly stated. Initial drug choice should be based on patient and clinician discussion to enable individualised patient care. **Reference** 1. American Diabetes Association (ADA), Standards of Medical Care in Diabetes 2015. January 2015. PDF online. http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/Documents/January%20Supplement%20Combined_Final.pdf; accessed 18 February 2015	caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
730	Merck Sharp and Dohme Ltd	NICE	General	1.6.19	**Repaglinide** MSD ask NICE to remove repaglinide from the proposed clinical guideline due to safety concerns, and limited use within current UK clinical practice/ market. A critical analysis of the draft CG87 highlighted clinical apprehension surrounding the use of repaglinide based on clinical experience in the UK and globally, and a recent meta-analysis showed the risk of hypoglycaemia was at least as great as that with sulfonylureas[1].	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors,

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					The SPC for repaglinide lists numerous safety concerns, for example a limited licence indication (in monotherapy or combination with metformin only), and a multiple dosing strategy up to 4 times daily, which will lead to adherence issues[2]. The medicines adherence guideline (NICE CG76, 2009) acknowledges the multifaceted problem of patient adherence; this guideline encourages good communication between health care professionals and patients when making decisions about medication choice and methods to support adherence[3]. The findings of O'Hare et al. 2015 substantiate the magnitude of adherence violations[1]. Similarly, Boccuzzi et al. 2001 reported decreased persistence of repaglinide (32.7%) at two years vs. metformin (53.8%). Repaglinide also had the highest rate of discontinuation in the first 12 months compared with metformin and sulfonylurea at 16.2%, 11.9%, and 11.3%, respectively[4]. The DVLA have also highlighted warnings for group 1 and 2 drivers who receive glinides (See comment 17) [5]. Repaglinide cannot be considered as standard of care in the UK. The following data support this statement: • An examination of IMS reported	pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, recommendations referring to repaglinide make clear in footnotes that "Repaglinide has a marketing authorisation for use only as monotherapy or in combination with metformin. Therefore, for people who cannot take metformin, there is no licensed combination containing repaglinide that can be offered at first intensification. Patients should be made aware of this when initial therapy is being discussed" and to "Be aware that initial drug treatment with repaglinide should be stopped and the drugs in the dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug." This information is also reflected in the algorithm.

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					standard units shows the decline of repaglinide use from 2,666 standard units in Q3 2011 to 2,102 standard units in Q3 2014. In contrast, metformin reported 448,972 and 528,268 standard units Q3 of 2011 and Q3 of 2014, respectively[6]. • Using IMS UK Disease Analyzer (MAT 2014) it was also possible to project national estimates of T2DM patients. The projected number of patients receiving either repaglinide or metformin nationally was 4,384 and 1,576,636 patients, respectively. The number of new initiations was markedly different. Of the new initiations for repaglinide (653 patients) and metformin (231,403 patients) only 0.3% was attributed to repaglinide[7]. • When GPs (n=101) were asked to consider prescribing repaglinide, 19% were not aware of any limitations associated with its use; whereas, 27% of GPs were concerned with hypoglycaemic events, and or liver disease (30%)[8]. Their apprehension and lack of awareness was further quantified by poor patient adherence. The survey results show that 81% of GPs thought that patients were somewhat likely or very likely to benefit from an	

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					individualised patient approach due to adherence concerns[8]. MSD believe that these concerns in addition to the barriers to implementation, discussed in comment 3, show that the use of repaglinide is not appropriate for T2DM patients, when other licenced alternatives are available. MSD would like to further understand the GDG assumption that repaglinide multiple dosing is comparable to metformin multiple dosing in terms of patient utility. The SPC for metformin states a dosing strategy of 2-3 times daily (max of 3g per day split between 3 doses)[9], whereas the SPC for repaglinide states a dosing strategy of 2-4 times daily (max of 16g per day split between 4 doses)[2]. This dose titration process will lead to repeated GP visits and additional costs. MSD queries what additional efficacy and safety data have contributed to NICE's decision to offer repaglinide in the 2015 clinical guideline vs. the 2009 decision not to include repaglinide; is this purely due to acquisition cost? MSD would like to understand if the additional burden on GP resources and associated costs were considered during the titration of repaglinide, which must be carefully monitored;	

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					namely in the elderly and patients with renal impairment. **Reference** 1. O'Hare, J et al. "The new NICE guidelines for type 2 diabetes- a critical analysis" Editorial, Available online. Br J Diabetes Vasc Dis 2015;15:xx-xx http://dx.doi.org/10.15277/bjdvd.2015.006; Accessed 18 February 2015 2. Prandin 0.5mg, 1mg, 2mg Tablets, Summary of product characteristics. EMC. February 2015. https://www.medicines.org.uk/emc/medicine/18980; accessed February 2015 3. NICE CG76, Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence. January 2009. https://www.nice.org.uk/guidance/cg76/chapter/1-guidance; accessed 18 February 2015 4. Boccuzzi, S et al. "Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population" Diabetes Care (2001) 24:1411–1415 5. DVLA, DVLA's current medical guidelines for professionals – conditions D to F. November 2014. https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-	

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					professionals-conditions-d-to-f ; accessed 18 February 2015 6. IMS Global National Sales Audit (Q311-Q314) 7. IMS Health UK, Disease Analyzer, Patients, MAT September 2014 as interpreted by MSD Ltd 8. MSD. Data on file. GP survey, clinical practice in type 2 diabetes patients February 2015 9. Glucophage 500 mg and 850 mg film coated tablets, Summary of product characteristics. EMC. January 2015. https://www.medicines.org.uk/emc/medicine/1043; accessed February 2015	
731	Merck Sharp and Dohme Ltd	NICE	General	1.6.20 1.6.22 1.6.23	**Pioglitazone** MSD request that when pioglitazone is recommended for use it is duly caveated with the relevant MHRA safety warnings and that an individualised approach is taken; this should involve discussion between both the patient and clinician to assess the added benefit vs. risk. **Safety concerns** The MHRA have published health warnings for pioglitazone, including an increased risk of bladder cancer and heart failure. • MHRA August 2011: The associated risk of bladder cancer in patients with T2DM was further examined in a	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are

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					European study. The findings show "a small increased risk of bladder cancer in patients taking pioglitazone; however, the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer"; the finding of this European study also report uncertainty "Whether the increased risk occurs early in treatment or only after prolonged exposure remains unclear"[1]. • MHRA January 2011: "A European review of the increased incidence of cardiac failure when pioglitazone is used in combination with insulin, especially in patients with **predisposing factors**, has recommended that the product information for insulin should equally reflect this risk and contain appropriate warnings. The product information for pioglitazone already contains warnings about its use in combination with insulin"[2]. In the full version of the guideline the GDG has given consideration to the safety concerns related to pioglitazone (Full Guideline, page 199, section 8.4.7), where they have made a specific request "that a cross reference to appropriate MHRA publications would also be appropriate". This has not been included in the NICE version	appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

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					and needs to be updated to include references to the relevant MHRA publications (as mentioned above). In addition to an increased risk of bladder cancer there are numerous contraindications for pioglitazone listed in the SPC[3], these include: • Hypersensitivity to the active substance • Cardiac failure or history of cardiac failure (NYHA stages I to IV) • Hepatic impairment • Diabetic ketoacidosis • Current bladder cancer or a history of bladder cancer • Un-investigated macroscopic haematuria. MSD have identified, using IMS UK Disease Analyzer, potential patient cohorts that would not be suitable for pioglitazone treatment based on SPC and MHRA contraindications. MSD is very concerned about how the use of pioglitazone will be safely implemented into such a complex patient population. The following values are a percentage of T2DM patients who are not eligible for pioglitazone. IMS UK Disease Analyzer, using a calculation to extrapolate to national levels, has been used to estimate the following values at a national level[3]. • Cardiac Failure (or history of) (NYHA stages I - IV), 3% (~82,500 patients)	

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					• All haematuria, 2% (~49,700 patients) • Bladder cancer - active or previous, 1% (15,000 patients) • Diabetic ketoacidosis, 1% (~22,900 patients) There are also numerous warnings associated with pioglitazone that may further limit its use in the T2DM population, as listed in the SPC[5]. Using IMS UK Disease Analyzer MSD has identified the following at risk patient groups[3]. If pioglitazone should be prescribed the balance of benefits and risks should be considered carefully both before and during treatment[3]: • patients with CVD, 22% (587,800 patients) • patients with osteoporosis/risk of bone fracture, 9% (233,500 patients) • patients with hepatic impairment/ liver disease, 3% (80,400 patients) • patients aged ≥65 years, 52% (1.4 million patients) These health warnings are supported by the findings of the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events)[6]. This randomised control trial, compared pioglitazone with placebo in 5,238 patients with T2DM who had evidence of macrovascular disease. At 3.5 years follow up, heart failure requiring and not requiring	

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					hospitalisation was significantly increased in the pioglitazone group compared with the placebo group (10.8% for pioglitazone vs. 7.5% for placebo (P=< 0.0001), and weight gain was greater in subjects in the pioglitazone group than in the placebo group (~3.6kg increase for pioglitazone vs. 0.4kg decrease in the placebo group)[6]. MSD refer the GDG to the 2009 CG87 clinical guideline, (paragraph 1.6.2.4, page 18)[7], which recommended "Do not commence or continue a thiazolidinedione (pioglitazone) in people who have heart failure, or who are at higher risk of fracture". MSD request that this wording is reinstated and highlighted in the interest of safety and individualised patient care. **Clinical practice** Pioglitazone is not considered to be the standard of care across the global market, with decreasing usage and withdrawals from several EU countries. Although pioglitazone has remained on the UK market, it is clear to see that pioglitazone use has been in steady declined since Q3 2011 (17,131 standard units) to Q3 2014 (11,561 standard units)[4]. To contextualise this, metformin reported 448,972 and 528,268 standard units Q3 of 2011 and Q3 of 2014, respectively[4].	

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					Using IMS UK Disease Analyzer (MAT 2014) it was also possible to project national estimates of T2DM patients. The projected number of patients receiving either pioglitazone or metformin nationally was 76,761 and 1,576,636 patients, respectively. The number of new initiations was markedly different during the 2014 MAT. Of the new initiations for pioglitazone (6,902 patients) and metformin (231,403 patients) only ~3% was attributed to pioglitazone[3]. The number of new initiations has reduced in 2014 at 6,902 patients compared with 2013 with 8,861 patients[3]. The French health authority (ANSM), withdrew all pioglitazone-containing products in June 2011 based on the findings of a small increased risk of bladder cancer in patients treated with pioglitazone observed in a French database study (CNAMTS) independently conducted by the French authorities[8]. Similarly, Germany issued a ban on new initiations with pioglitazone (including fixed dose combinations with pioglitazone) in patients funded by statutory insurance (2010). The GBA followed the recommendations of an IQWIG assessment that showed pioglitazone was inferior to existing alternatives[9]. The results of our recent GP (n=101 GPs)	

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					survey show that when asked to consider prescribing pioglitazone GPs recalled numerous limitations; this included but was not limited to: heart failure (76%), risk of bladder cancer (42%), liver disease (32%), renal disease (30%), and a risk of fractures (23%)[10]. These limitations were not mutually exclusive, and GPs often recalled multiple risk factors. These findings in addition to the barriers to implementation, as listed in comment 3, suggest that the ability of GPs to offer an individualised patient approach with the proposed clinical guidelines would not be feasible, and would negatively impact on patient safety. **Reference** 1. MHRA Drug safety update, Pioglitazone: risk of bladder cancer. August 2011. https://www.gov.uk/drug-safety-update/pioglitazone-risk-of-bladder-cancer; accessed 18 February 2015 2. MHRA Drug safety update, Insulin combined with pioglitazone: risk of cardiac failure. January 2011. https://www.gov.uk/drug-safety-update/insulin-combined-with-pioglitazone-risk-of-cardiac-failure; accessed 18 February 2015 3. IMS Health UK, Disease Analyzer, Patients, MAT September 2014 as	

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					interpreted by MSD Ltd 4. IMS Global National Sales Audit (Q311-Q314) 5. Actos Tablets, Summary of product characteristics. EMC. June 2014.https://www.medicines.org.uk/emc/medicine/4236; accessed 18 February 2015 6. Dormandy, A et al. "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial" Lancet. (2005) (9493):1279-89 7. NICE CG87, Type 2 diabetes: The management of type 2 diabetes. May 2009. https://www.nice.org.uk/guidance/cg87; accessed 18 February 2015 8. AFSSAPS, Use of Medications Containing Pioglitazone (Actos®, Competact®) Suspended. June 2011. http://ansm.sante.fr/var/ansm_site/storage/original/application/4e293bcd0814c025b94d46d7502a0958.pdf; accessed 18 February 2015 9. IQWIG, Glitazones in the treatment of diabetes mellitus type 2. February 2005. https://www.iqwig.de/download/A05-	

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					05A_Executive_Summary_Glitazones_in_the_treatment_of_diabetes_mellitus_type_2.pdf; accessed 18 February 2015 10. MSD. Data on file. GP survey, clinical practice in type 2 diabetes patients February 2015	
729	Merck Sharp and Dohme Ltd	NICE	General	1.6.21 1.6.22 1.6.23 1.6.26 1.6.27	**DPP-4i prescribing detail** MSD ask the GDG to be consistent with their approach to prescribing; and this should follow license indication and not cost. MSD commend the prescribing detail for GLP-1s, which follows and individualised patient approach. The phraseology reported in section 1.6.29 of the NICE guideline states "base the choice of GLP-1 mimetic on the person's preference after discussing the risk and benefits of each licenced option". MSD request that NICE use a similar approach when recommending the use of DPP-4i's. MSD suggest the following statement "*when a DPP-4i is preferred, base the choice of DPP-4i on the patients' preference after discussing the risks and benefits of each licenced option".* The choice of DPP-4i should be based on licenced indication, individualised patient care and preference, and should only reflect those interventions considered within the cost-utility analysis.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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732	Merck Sharp and Dohme Ltd	NICE	General	1.6.21 1.6.22 1.6.2	**<u>Sulfonylurea</u>** MSD ask that additional prescribing information are provided for at risk groups when considering the use of sulfonylureas, i.e. patients with renal impairment, and those who are at increased risk of hypoglycaemia. The GDG have clearly acknowledged the risks associated with sulfonylureas by removing their automatic use at first intensification, and this should be commended. MSD request that the guideline clearly defines patient populations that are not suitable for sulfonylureas at each stage of treatment intensification. An individualised patient approach should be adopted and the added benefits and risk should be clearly communicated; i.e. T2DM who drive frequently or for an occupation should not be prescribed sulfonylureas (see comment 17 for DVLA warnings). The SPC lists the following contraindications[1]: • diabetes complicated by ketosis or acidosis • diabetics undergoing surgery, after severe trauma or during infections • diabetic pre-coma and coma • patients with severe renal or hepatic insufficiency • patients treated with miconazole	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

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					• women who are lactating MSD would like to draw the GDGs attention to the growing wealth of evidence that shows sulfonylureas have adverse cardiovascular effects. MSD strongly believe data for cardiovascular risk have not been given adequate consideration in the decision making process. The systematic review and meta-analysis, described below, is supported with extensive retrospective UK observational data, which could be considered the most representative of clinical practice as this reflects gliclazide use. • Monami et al. 2013[2] reported the results of a systematic review and meta-analysis that examined cardiovascular safety of sulfonylureas. A total of 62 RCTs with a duration of at least 6 months contributed to the major cardiovascular events (MACE) and mortality outcomes. Their analysis showed significantly increased risk for mortality (OR: 1.22 [1.01;1.49]) and stroke (OR: 1.28 [1.03;1.60]) in patients treated sulfonylurea vs. other oral anti-hyperglycaemic agents. The results show that the risk of stroke increased significantly when sulfonylurea was compared with DPP-4i alone (OR: 4.51 [1.65;10.79]). The authors concluded	

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					that in T2DM, the use of sulfonylureas is associated with increased mortality and a higher risk of stroke[2]. • Morgan et al. 2014[3] a UK retrospective study in CPRD, reported all-cause mortality and MACE outcomes using the CPRD in patients prescribed either a sulfonylurea (N=33,983) or DPP-4i (N=5,447). The results show increased MACE events for sulfonylurea patients vs. DPP-4i at 11.3 and 5.3 events per 1,000 patient years, respectively. Similarly increased all-cause mortality rates were observed in patients treated with sulfonylurea vs. DPP-4i at 16.9 and 7.3 per 1,000 patient years, respectively. The authors concluded that there was a reduction in all-cause mortality for patients treated with metformin combined with DPP-4i versus metformin plus sulfonylurea, and a similar trend for MACE[3]. • Bannister et al. 2014[4] used observational data from the CPRD in patients with T2DM treated with metformin or sulfonylurea monotherapy vs. matched controls without diabetes. The results of this study show increased mortality associated sulfonylurea monotherapy vs. matched controls at 50.9 and 28.7 deaths per 1,000 person	

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					years, respectively; this was higher than metformin at 14.4 per 1,000 patient years. The authors concluded that patients treated with a sulfonylurea had markedly reduced survival compared with both matched controls and those receiving metformin monotherapy[4]. When asked to consider prescribing a sulfonylurea GPs recalled the following limitations: risk of hypoglycaemia (74%), intolerance to a sulfonylurea (59%), BMI≥35 (43%), and elderly patients 75+ (41%). These limitations were not mutually exclusive, and numerous GPs selected more than one. MSD believes that these data support the immediate downgrading of sulfonylureas at treatment initiation and first-intensification[5]. **Reference** 1. Gliclazide Tablets BP 80mg, Summary of product characteristics. EMC. April 2011. http://www.medicines.org.uk/emc/medicine/24126; accessed 18 February 2015 2. Monami, M et al. "Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials". *DOM*, 15: (2013) 938-953. 3. Morgan, C eta l. 2Combination therapy with metformin plus sulphonylureas	

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					versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality" Diabetes, Obesity and Metabolism 16: (2014) 977–983. 4. Bannister, C et al. "Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls" Diabetes, Obesity and Metabolism 16: (2014) 1165–1173. 5. MSD. Data on file. GP survey, clinical practice in type 2 diabetes patients February 2015	
735	Merck Sharp and Dohme Ltd	NICE	General	1.6.22	**First intensification** MSD ask that the treatment options available at first intensification reflect the removal of repaglinide due to safety concerns (see comment 9). MSD insist that patients who have failed to achieve adequate HbA1c control on: • metformin should be offered either a DPP-4i **or** thiazolidinedione **or** sulfonylurea according to patient suitability and preference in discussion with their clinician. • either sulfonylurea **or** pioglitazone **or** a	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which

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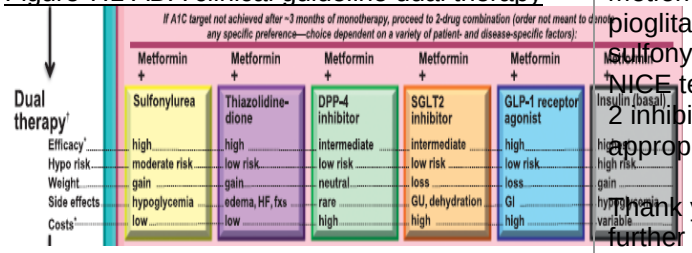
					DPP-4i are offered one of the remaining therapies; again this should be based on patient suitability and preference in discussion with their clinician. A similar approach has been adopted in the ADA 2015 guideline "If the HbA1C target is not achieved after approximately 3 months, consider a combination of metformin and one of these six treatment options: sulfonylurea, thiazolidinedione, DPP-4i, SGLT-2, GLP-1 receptor agonists, or basal insulin"[1]. This promotes greater flexibility for both patient and clinician. Figure 7.1 ADA clinical guideline dual therapy  MSD request that recommendations for DPP-4i's at first intensification reflect the cost effectiveness evidence considered (sitagliptin, vildagliptin, and linagliptin) in line with licensed indication (see comment 5, table 1)	pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate. Thank you for this comment, which calls for further analysis on repaglinide. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on

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					MSD are concerned that the GDG have not evaluated the implications of treatment switching for repaglinide at first intensification, and that blanket prescribing does not adopt an individualised patient approach. Have the GDG fully considered: • The additional costs associated with testing and monitoring during the removal of repaglinide and addition of two new oral agents that would need to be added in a stepwise manner. • The risk of losing HbA1c control during the stepwise addition of two drugs • The risk of potential short- and long-term safety outcomes i.e. weight gain, CV morbidity etc. • The impaired quality of life of these patients. MSD asks that the GDG consider their own call to research (section 2.1 NICE draft CG87 (2015)), and that in the absence of these data the GDG cannot justify the unknown risks associated with repaglinide treatment switching when there are licensed alternatives that do not require this. • NICE future research question '*There is limited understanding of the short- and long-term effects of stopping a therapy and switching to another in terms of diabetes control (HbA1c levels),*	pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.

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					hypoglycaemic risk, weight gain, and cardiovascular morbidity and mortality. In addition, there is limited understanding of how quickly consideration should be given to stopping and switching to another drug treatment and, if stopping and switching may be needed, what the optimal sequencing is of drug treatments' (NICE Draft CG87, page 33, section 2.1)**.** MSD would also refer the GDG to the quality of evidence presented at first intensification, which demonstrates uncertainty around the most suitable treatment option. • The full guidance document presented low quality evidence for hypoglycaemia at study end point and change in body weight. The quality of evidence for adverse events at study end point, and change in blood glucose was considered moderate to low, and moderate, respectively. • The GDG reported in section 8.4.10.2 of the full guidance document that the original economic analysis had potentially serious limitations. **Reference** 1. American Diabetes Association (ADA),	

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					Standards of Medical Care in Diabetes 2015. January 2015. PDF online. http://professional.diabetes.org/admin/UserFiles/0%20-%20Sean/Documents/January%20Supplement%20Combined_Final.pdf; accessed 18 February 2015	
736	Merck Sharp and Dohme Ltd	NICE	General	1.6.27	**Second Intensification** MSD ask that the treatment options and wording for the recommendation of medications at second intensification reflect: • The removal of repaglinide at drug initiation (see comment 9). • The use of each drug class at drug initiation and first intensification, and is in line with licenced indication and patient/ clinical preference, suitability, and should only recommend those considered within the cost-utility analysis. • Evidence for sitagliptin only. This was the only DPP-4i evaluated at second intensification and the recommendation within the NICE guideline should reflect this. MSD insist that the treatment algorithm is amended to reflect the full licence of sitagliptin, which can be used in combination with metformin + pioglitazone (see comment 15).	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations.

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740	Merck Sharp and Dohme Ltd	Appendix F	General	Table 59	Model price inputs To undertake the cost-utility modelling produced in this guideline, costs related to microvascular and macrovascular complications have primarily been taken from the UKPDS randomised clinical trial. The group have inflated the prices, as standard, to the latest cost year (2012/13) using a source year of 2000. In the original publication, the costs for in-patient admissions were based on an average of the Department of Health's NHS Trust Financial Returns for 1997/98 and 1998/9. Non-inpatient costs were derived from units cost publication from PSSRU 1999 and UKPDS clinics. It would appear that the more appropriate source year to use for these costs is 1998 or 1999 rather than 2000. The cost of complications should be readjusted to reflect this and then the cost-utility analyses re-run to reflect the costs more appropriately. **Reference** 1. Clarke, P et al. "The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes ". Diabetic Medicine, 20: (2003) 442-450.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
147	National Diabetes Nurse Consultant	NICE			The use of SGLT-2 s - Can you be more specific about the use of these agents in reducing HbA1c and in reducing weight ?HCPs will not want to keep checking all the different guidelines	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-

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	Group				as they have limited consultation time	references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
110	National Diabetes Nurse Consultant Group	NICE FULL	11 and throughout 12 and throughout	1	Why are % readings being included in this document HbA1c measurement switched to mmols/mol in 2011 which is referenced in point 1.6.2 and laboratories only present results in mmol/mol. The continued used of % 4 years after the change is promoting the use of outdated terminology.	Thank you for your comment. To ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that they remain within the guidance. Therefore both the mmols per mol and percentage readings have been retained.
111	National Diabetes Nurse Consultant Group	NICE	11	15 5	HbA1c targets of 53mmol/mol may increase the numbers experiencing hypoglycaemia and subsequent ambulance callout and particularly if used in people with a long duration of diabetes	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
112	National Diabetes Nurse Consultant	NICE Full	11 12	22 5	"Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this

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	Group				and agree how it should be interpreted and acted upon" has been removed from the guidance but continues to form part of the curriculum for the structured education process recommended in 1.3.1	evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. NICE anticipates that diabetes education and curriculums for healthcare professionals will change and continue to develop based on the latest review of the best available evidence.
114	National Diabetes Nurse Consultant Group	NICE	11	23 -25	This will include older people including the frail elderly, and drivers if Rapaglinide is prompted as first or 2nd line treatment - Hypo information will need to be given and leaflets along with blood glucose monitoring equipment and training	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
113	National Diabetes Nurse Consultant Group	Full	12	18	No mention of if patients are symptomatic that a sulphonylurea should be commenced (p 20 line18, point 46	Thank you for your feedback. Recommendation 46 in the full guideline (or 1.6.15 in the NICE version) states: "*If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin (see recommendations 63–65) or* ***a sulfonylurea****, and review treatment when blood glucose control has been achieved.*"
118	National Diabetes Nurse Consultant	Full	12	21	If repaglinide has been effective but the natural deterioration in glycaemic control occurs due to the progressive nature of type 2 diabetes and an additional drug is required but repaglinide has to	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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	Group				be stopped prior to commencing the additional treatment it would need to be replaced with an equivalent dose of sulphonylurea first to prevent a marked deterioration in glycaemia control. This is complicating the treatment pathway and introducing high risk of significant periods of marked deterioration of control.	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The health economic model had annual cycles and was not structured to consider short term deterioration in control that could occur when switching or intensifying treatment options.
115	National Diabetes Nurse Consultant Group	Full	12	4 9-23	The initial dose of Repaginide is 0.5mg titrated every 2 weeks to maximum single dose of 4mg and total daily dose of 16 mg (4mg ODS) to facilitate this dose titration regular BG monitoring will be required to identify need for dose titration of frequency of dosing. The need for 3-4 times daily dosing will have negative impact on adherence and goes against the recommendations in the **medicines adherence guidance** referenced on page 12 line 4 which states 1.1.22 "Be aware that patients may wish to minimise how much medicine they take." For many patients this relates to not only the number of different tablets they take but the actual number of tablets they take. **1.2.8** "simplifying the dosing regimen" Repaglinide is complicated as the dosing regimen needing to be taken TDS for the maximum prescribable dose to be given and if	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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					4mg is given once daily instead of 2mg BD or 1mg/1mg/2mg to spread effect across the day to address BG profile can cause significant hypoglycaemia- tablets are 0.5mg,1mg and 2mg tablets with need for different doses at different meal- a single dose of 4mg if applicable which is rare is at least 2 tablets maximum dose id 8 tablets daily. If doses are increased in the 0.5 mg dose increments recommended patients could be using 2 or 3 different dose of tablets.	
116	National Diabetes Nurse Consultant Group	NICE	12	8	This medication (Rapaglinide) is strongly associated with hypoglycaemia - so individuals may need to blood glucose monitor - any cost saving would therefore be lost. and particularly if the user has a severe hypo leading to ambulance call out or hospital admission of which the risk is increased if a once daily dose titration is adopted without supportive blood glucose monitoring This preparation should probably come with a warning about using it or sulphonylureas in Dosett boxes as people using these aids are usually forgetful, frail and/or elderly. If the individual decided not to eat at the time this medication was due they may not have the capacity to know which tablet is a sulphonylurea, and hence would take all the drugs in the dossett box scheduled for that time – this would put them at risk of hypoglycaemia	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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					The manufacturers own guidance states driving guidance as :If you are a driver you should take special care, as your ability to concentrate may be affected if your diabetes is not well controlled. You may be advised to check your blood sugar levels before you travel and to have a snack with you on long journeys.	
117	National Diabetes Nurse Consultant Group	NICE	12	9	The addition of Pioglitazone in this predominately older population is a real risk – as heart failure rates in people with diabetes are increasing year on year (Diabetes UK State of the Nation 2015). This drug cannot be used in that population and this medication should be used with caution in post menopausal women due to risk of bone fractures- this significantly reduces the number of patients it could be recommended for. Ref :- CMAJ. 2007 Sep 25; 177(7): 723–724. doi: 10.1503/cmaj.071177 PMCID: PMC1976649 Health and Drug Alerts **Diabetes drug pioglitazone (Actos): risk of fracture** Reza Heidarpour Meymeh, MD* and Eric Wooltorton, MD MSc†Product characteristics from https://www.medicines.org.uk/emc/medicine/4236 state: In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

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					patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Also concern for those in who weight gain would cause an issue ie the increased risk of sleep apnoea and other weight related comorbidities due to the weight gain possible experienced from this medication. Ref. Product Characteristics https://www.medicines.org.uk/emc/medicine/4236 state - *Weight gain* In clinical trials with pioglitazone there was evidence of dose related weight gain, which may be due to fat accumulation and in some cases associated with fluid retention. In some cases weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet. Reference is made to tolerability of pioglitazone but not efficacy- whilst in patients with significant Insulin resistance this drug can have a marked effect on their HbA1c on other patients it will have no impact and therefore should be stopped prior to a further medication being commenced.	

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122	National Diabetes Nurse Consultant Group	NICE	13	14	1.1.1 This section is too vague- Please can you add in more specific information re co-morbidities and glycaemic targets in line with other national and international guidance such as Diabetes UK- end of life guidance, The ADA medical standards 2015, The IDF care of older people with type 2 DM, The Association of Geriatricians 2013	Thank you for your feedback. Consideration was given to being more specific in this section. However, this was balanced against the need to ensure that the approach to care is individualised, taking into account a range of patient specific factors. The need for indivualisation of care, and the wide range of factors that need consideration prevented the creation of more specific information.
119	National Diabetes Nurse Consultant Group	Full	13	General	**Initial therapy algorithm** % results should not be included in the algorithm No mention in this algorithm that a SU should be commenced if symptomatic see p20 line 18 point 46 % results should not be included in the algorithm (see first point) SGLT 2's need to be included in this algorithm or will be of no benefit to clinicians. Patient preference mentioned in relation to Repaglinide and DPPIV and SU but not pioglitazone. If Metformin contraindicated then all drug groups should be an option based on contraindications or patient preference	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that both mmols per mol and percentage readings are included. The algorithms have been simplified to a single A4 page and rescue treatment with insulin or a sulfonylurea added. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the

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						technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
120	National Diabetes Nurse Consultant Group	Full	14	General	**First Intensification algorithm** % results should not be included in the algorithm Patient preference only appears to be an option if Metformin contraindicated as first line therapy Not clear on algorithm that repaglinide to be stopped if commenced as first line at this point Although Pioglitazone may have been declined as initial therapy for weight reasons it may be preferable to patients over an SU at first intensification but not present as an option for those on DDP IV	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that both mmols per mol and percentage readings are included. The guideline development group has reflected

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					SGLT 2's need to be included in this algorithm or will be of no benefit to clinicians. Nothing about stopping any of the medication if ineffective- DPPIV and Pioglitazone does not have a positive impact on all patients HbA1c- if no response should be stopped and alternative treatment started rather than addition of third treatment	on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The algorithms have been simplified to a single A4 page with a footnote specifically stating that repaglinide would need to be stopped and switched at first intensification. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The guideline includes a generic recommendation 1.1.1 (NICE version) that states "…*Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
121	National Diabetes Nurse Consultant Group	Full	15	General	**Second Intensification algorithm** % results should not be included in the algorithm This looks like patients on Metformin and DPPIV have to go straight to Insulin, does not appear to be an option to add in SU. Tolerated include but not efficacy. Nothing about	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be

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					stopping any of the medication if ineffective- DPPIV does not have a positive impact on all patients HbA1c- if no response should be stopped and alternative treatment considered rather than addition of Insulin SGLT 2's need to be included in this algorithm or will be of no benefit to clinicians. The insulin flow looks like it should go NHP change to detemir change to glargine change to Biphasic mix- detemir and Glargine should be a box together as an alternative to NHP Biphasic mix should be linked to HbA1c- as in p23 line 25 What is the difference between Biphasic or other pre-mixed insulins – need to use biphasic or pre-mixed consitently	familiar with percentages, it is important that both mmols per mol and percentage readings are included. At second intensification, the guideline development group has recommended the following for people who can take metformin: metformin+pioglitazone+sulfonylurea, metformin+sulfonylurea+DPP-4 inhibitor and starting insulin-based treatments; and for people who cannot take metformin: starting insulin-based treatments. The guideline includes a generic recommendation 1.1.1 (NICE version) that states "…*Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug

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						therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The algorithms have been simplified to a single A4 page with detailed information on insulin-based treatments. Term has been changed to "pre-mixed (biphasic) human insulin" for consistency.
123	National Diabetes Nurse Consultant Group	Full	18	38 and 40	At target should be used rather than stable	Thank you for your feedback. The phrase "stable" has been retained.
124	National Diabetes Nurse Consultant Group	Full	19	13	RECOMMENDATION TO USE REPAGLINIDE goes against the recommendations in the **medicines adherence guidance** referenced on page 12 line 4 which states 1.1.22 "Be aware that patients may wish to minimise how much medicine they take." For many patients this relates to not only the number of different tablets they take but the actual number of tablets they take. **1.2.8** "simplifying the dosing regimen" repaglinide is complicated dosing regimen needing to be taken QDS for the maximum prescribable dose to be given and if 4mg is	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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				43	given once daily instead of 2mg BD or 1mg/1mg/2mg to spread effect across the day to address BG profile can cause significant hypoglycaemia- tablets are 0.5mg,1mg and 2mg tablets with need for different doses at different meal- a single dose of 4mg if applicable which is rare is at least 2 tablets maximum dose id 8 tablets daily. If doses are increased in the 0.5 mg dose increments recommended patients could be using 2 or 3 different dose of tablets. All drivers on Repaglinide will need to BG monitor	
125	National Diabetes Nurse Consultant Group	NICE	19	25	Have you considered the risk of hypoglycaemia in people with diabetes trying to attain these targets (53mmol/mol if on insulin, Rapaglinide or sulphonylureas	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
127	National Diabetes Nurse Consultant Group	NICE	20	10	The use of SU and now of repaglinide will mean any small cost savings made using these drugs for most with Type 2 DM will easily be offset with costs related to ambulance call outs and hospital admission	Thank you for your feedback. NHS costs relating to severe hypoglycaemic episodes were fully considered in the health economic modelling (see full guideline 8.4.3). These included estimates of the proportion of severe hypoglycaemic episodes that required GP

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						admissions, ambulance call outs, A&E attendance and/or hospital admissions.
128	National Diabetes Nurse Consultant Group	NICE	20	15	What does this sentence actually mean - see previous comments	Thank you for your feedback. As indicated by multiple stakeholders, people who are older or frail may be at a greater risk of tight glycaemic control. Hence, the recommendation highlights that specific consideration should be given to these clinical circumstances.
129	National Diabetes Nurse Consultant Group	NICE	20	18	The amount of patients accessing emergency care for hypos due to low HbA1c's is increasing as are admission rates - a range for HbA1c for those using insulin , Rapaglinide and SU should be stated- local audit of 106 ambulance call out in 94 people over 16 weeks showed that 50% had an HbA1c lover than 58 mmol/l and 10% were lover than 42 mmol/l	Thank you for your feedback. NHS costs relating to severe hypoglycaemic episodes were fully considered in the health economic modelling (see full guideline 8.4.3). These included estimates of the proportion of severe hypoglycaemic episodes that required GP admissions, ambulance call outs, A&E attendance and/or hospital admissions.
131	National Diabetes Nurse Consultant Group	Full	20	46	This point is completely missed from the algorithm	Thank you for your feedback. The algorithm has been simplified to a single A4 page, including rescue treatment with insulin or sulfonylurea illustrated.
126	National Diabetes Nurse Consultant Group	NICE	20	5	1.6.9 needs to be more specific in respect of reduced life expectancy - there should be no HbA1c targets for individuals experiencing the last year of life (See Diabetes UK ADA and European guidance) People in care homes with or without dementia are now considered as being in end of life care as are the frail elderly – the ADA and IDF offer specific information on glycaemic targets for those with other comorbidities	Thank you for your feedback. The recommendation provides general guidance on circumstances in which consideration should be given to relaxing blood glucose targets. The guideline development group has not reviewed evidence on the withdrawal of HbA1c targets for people with reduced life expectancy and did not consider it appropriate to provide specific guidance in the absence of evidence.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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130	National Diabetes Nurse Consultant Group	Full	20	6	Consider short term should be replaced with commence self monitoring for the duration of treatment with....	Thank you for your feedback. The phrase "short-term" has been kept in the amended recommendation: "*Consider short-term self-monitoring of blood glucose levels (and review treatment as necessary):* • *when starting treatment with oral or intravenous corticosteroids* ***or*** • *to confirm suspected hypoglycaemia.*"
135	National Diabetes Nurse Consultant Group	Full	21	16	The need to stop repaglinide when first intensification needed and the complex dose titration is delaying the important achievement of excellent glycaemic control to enable individuals to benefit from the protection offered by the metabolic memory	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
134	National Diabetes Nurse Consultant Group	NICE	21	27	1.6.16 this implies that Metformin has to be commenced on all individuals even if have a low BMI	Thank you for your feedback. Metformin can be offered to individuals whose blood glucose levels are inadequately controlled by diet and lifestyle interventions only, irrespective of BMI.
136	National Diabetes Nurse	Full	21	28	What if pioglitazone has no impact on HbA1c were is the guidance to stop it	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they

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	Consultant Group					do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
132	National Diabetes Nurse Consultant Group	NICE	21	3	This could mean most people with Type 2 DM on SUs or Rpaglinide who drive will need to test	Thank you for your feedback. The recommendation notes that individuals on oral medications that may increase the risk of hypoglycaemia while driving or operating machinery should be considered for self-monitoring as per the DVLA guidance.
137	National Diabetes Nurse Consultant Group	Full	21	36	What if DPPIV has had no impact on Hba1c were is the advice to stop it.	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
138	National Diabetes Nurse Consultant Group	Full	21	57	What if SU has had no impact on Hba1c were is the advice to stop it.	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping

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						rules from the previous iteration of the guideline, CG87.
133	National Diabetes Nurse Consultant Group	NICE	21	8	Consider to be replaced with commence bself bllod glucose monitoiring for the duration of treatment..... Diabetes and steroids - Please check the JBDS management of hyperglycaemia for people taking gluco-corticosteroids - all should be blood glucose testing	Thank you for your feedback. As there was no evidence to suggest that patients on corticosteroids should self-monitor, a strong recommendation of "Commence" cannot be applied and therefore the term "Consider" has been used.
140	National Diabetes Nurse Consultant Group	NICE	22	11	Please state where Metformin sustained release fits in with this?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
141	National Diabetes Nurse Consultant Group	NICE	22	13	Please see previous comment - there should be provisos on the individuals where Rapaglinide or Sulphonylureas would not be suitable - The ADA have an excellent algorithm showing side effects of all drug classes which if replicated for the UK would benefit HCPs in the decision making process	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see

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						MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
142	National Diabetes Nurse Consultant Group	NICE	22	25	Please state patients who would be at increased risk of hypos and or weight gain when using the SU- Also please advise on the use of a SGLT-2 inhibitor and where it sits in this pathway	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the

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						technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
139	National Diabetes Nurse Consultant Group	Full	22	40	What constitutes specialist care	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
145	National Diabetes Nurse Consultant Group	NICE	23	18	Not clear repaglinide to be stopped	Thank you for your feedback. As stated in recommendation 1.6.23 (in NICE version) "*When switching from repaglinide to any of these combinations, introduce the 2 new medicines in a stepwise manner, checking for tolerability of each*", repaglinide should be stopped and switched.
144	National Diabetes Nurse Consultant Group	NICE	23	22	Where do SGLT-2 Inhibitors fit in or GLPI receptor agonists?	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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						TA guidance. Please see recommendations 1.6.29, 1.6.30 and 1.6.31 in the NICE version for the position of GLP-1 mimetics.
143	National Diabetes Nurse Consultant Group	NICE	23	3	Is the drug with the lowest acquisition cost the most effective?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
146	National Diabetes Nurse Consultant Group	NICE	24	3	Use of Pioglitazone – There should be proviso's around it use such as : Or if the individual has heart failure or previous history of bladder cancer or is post menopausal or where an increase in weight is undesirable	Thank you for your feedback. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
148	National Diabetes Nurse Consultant Group	NICE	25	10	Please be more specific around the licensing for non oral diabetes drugs The licenses are different for all these agents so the lowest cost drug many not be suitable for all	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs,

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						available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
149	National Diabetes Nurse Consultant Group	NICE	25	26	Do you mean sleep apnoea if so please be specific	Thank you for your feedback. The guideline development group considered the generic phrase "other medical problems associated with obesity" adequate, not requiring an exhaustive list of examples of relevant conditions.
151	National Diabetes Nurse Consultant Group	NICE	26	10	If the patient has lost the weight and not reduced HbA1c there are still health benefits re cardiovascular that should be taken into account	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
152	National Diabetes Nurse Consultant Group	NICE	26	12	Specialist care needs to be defined in relation to suitable trained HCP not location Suitably trained HCPs in intermediate care or enhanced practice are capable of caring for these individuals and in many service design models do in fact care for these people, without involvement of secondary care which would be historically considered to be specialist care	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
15	National	NICE	26	27	Suggest include insulin safety advice and driving	Thank you for your feedback. Referral to DVLA

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3	Diabetes Nurse Consultant Group				advice in this section	guidance has been added to the recommendation
150	National Diabetes Nurse Consultant Group	NICE	26	6	Are they all equally effective? There is evidence that the cheapest is not always the most effective	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
154	National Diabetes Nurse Consultant Group	NICE	27	1	1.6.33 this reads that all other OHA should be stopped YET for NPH once daily or OTHER basal insulin to be effective it will need to used in combination with OHA IN addition to Metformin- if this recommendation means that insulin must only be used with Metformin then the insulin recommendations will need to be amend.	Thank you for your feedback. The recommendation (1.6.32, NICE version) has been amended to: "*When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.*" for greater clarity.
155	National Diabetes Nurse Consultant Group	NICE	27	9	Where does Degludec fit with this?	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in

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						appendix F table 58. Insulin degludec-metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec-metformin, and subsequently it does not appear in the algorithm.
156	National Diabetes Nurse Consultant Group	NICE	30	10	There needs to be specific clear guidance on diabetes and CKD in this document and especially around screening and monitoring ; and also the use of oral diabetes medications where dose reduction or use with caution or non use depending on CKD function varies between same class medication Where is the guidance of when to refer to specialist care? HCPs need this guidance in this document as they are unlikely to pull off the renal guidance	Thank you for your feedback. The recommendations on chronic kidney disease have been updated by the recently published guideline on Chronic Kidney Disease. NICE anticipates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. This function links all related NICE guidance on a topic area and should assure quick navigation between recommendations on type 2 diabetes and chronic kidney disease.
157	National Diabetes Nurse Consultant Group	NICE	General	General	This guidance is at odds with all other international and some UK specific guidance – the pathways are confusing as is the treatment algorithms in the full guidance and will not be helpful to HCPs working with individuals with diabetes.. The use of medications which can lead to hypoglycaemia or weight gain without deference to clear safety information is concerning as is the unclear guidance on glycaemic targets – The ADA information regarding agreed targets depending on clinical need, co-morbidities and	Thank you for your feedback. The guideline recommends 2 HbA1c targets: 1) 48 mmol/mol (6.5%) for people managed on diet/lifestyle or in combination with a single drug not associated with hypoglycaemia (see recommendation 1.6.7 in NICE version). 2) 53 mmol/mol (7%) for people who require drug intensification (see recommendation 1.6.8 in NICE version). However, the guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE

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					other factors such as motivation, duration of diabetes is clear and concise and it would be beneficial if this was in this UK guidance. Primary care practitioners are unfamiliar with repaglinide and without significant education which will need to be funded as will not be support by companies producing repaglinide as off patent could result in a significant increase in hypoglycaemia or periods of poor control due to poor titration and need to stop at second intensification. The failure to include SGLT2 in recommendations means that this guidance in relation to glycaemic management will be incomplete and the algorithms will be of no clinical benefit to HCP and will need to be rewritten local to reflect all guidance As this draft recommendation stands justifying the conclusion made and teaching and training in particular non specialist clinicians when the guidance is not in sinc with other international recommendation would be challenging and probably inappropriate	version) to individualise and agree targets. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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						TA guidance.
640	Newcastle Hospitals NHS Trust	Full	123	l 42, rec 40	This discrimination in regard of the elderly is unacceptable. Indeed later the document notes (p 122 8.1.3) 'The GDG thought that, when agreeing target values with adults with type 2 diabetes, it is more important to consider the nature of the individual's current medical condition – that is, diabetes, its complications and any other comorbidities – rather than age alone.' Quite! There are rather a lot of unnecessary references to older people in this document. Plenty of people of younger age are similarly vulnerable.	Thank you for your feedback. Many stakeholders have highlighted the increased risk of adverse effects (such as hypoglycaemia) of tight glycaemic control particularly in older or frail individuals. The guideline development group has also highlighted other cirumstances when HbA1c targets should be relaxed (see Recommendation 1.6.9 in NICE version).
657	Newcastle Hospitals NHS Trust	Full	124	l 1 et seq section 8.2 (whole)	This is most odd, as essentially the question is answered and dealt with already in 8.1. Furthermore terminological bias is introduced here, as much of what is called 'intensive' is now usual practice as section 8.1 recognizes, and most of what is meant by 'conventional' is better termed 'historic'. It would be better to integrate this section with 8.1 as they address the same question, allowing the recommendations of 8.1 to stand. Often the difference in glucose control within the studies cited is only around 1.0 % (11 mmol/mol) HbA_{1c}, and the meta-analyses wrongly concatenate studies of people in very different circumstances (UKPDS, newly diagnosed, long study duration; DIGAMI, post-MI, and short study duration; UGDP, historic therapy with failed randomization; etc). Basically the evidence analysis here is very poor	Thank you for your feedback. Although it is recognised that the collective evidence informed the overall recommendations, because sections 8.1 and 8.2 included different types of studies, it was necessary to undertake these reviews separately. The guideline development group noted the lack of consistency in the definition of intensive and conventional targets and that this differed between included studies which may have changed over time. Due to the potential for confusion by the indeterminate nature of intensive and conventional terminology, the group agreed that HbA1c target values should be provided without any attempt to dichotomise into either group. Therefore, all the recommendations for target values are included in Section 8.1.4 in the full guideline. The analysis for Section 8.2 is derived from a Cochrane systematic review.

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					quality indeed, and the meta-analysis would not be publishable. A more intelligent Bayesian approach using some of the modern studies excluded would have been more sensible, though not easy and not previously attempted.	Overall, the levels of heterogeneity were considered to be acceptable (see forest plots in Appendix D). However, where heterogeneity was considered to be serious or very serious, the quality was downgraded in the GRADE assessment.
633	Newcastle Hospitals NHS Trust	Full	14 15	algorithms	These algorithms are even more complicated and less easy to follow than those of CG66/87. The minds of the people who draw these clearly work in different ways from most health care professionals. Have a look at the simpler format used by the International Diabetes Federation and Chinese Diabetes Society. They are comprehensible unlike these diagrams.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
658	Newcastle Hospitals NHS Trust	Full	166	l 23 and other section 8.4	There is an important terminological problem with this section. It refers to stepped therapy as 'intensification'. There is nothing intensive about taking two glucose lowering therapies once HbA_{1c} has deteriorated to above 53 mmol/mol, any more than taking two anti-hypertensives if your BP is above 140 mmHg systolic. The use of this term gives the wrong educational message. Intensification would be adding another agent to someone already in adequate control. To describe appropriate prescription of one drug as an intensive action is misleading.	Thank you for your feedback. The guideline development group gave much consideration on the terminology used. Options such as "first/second line", "phase" or based on numbered agents (mono, dual) were considered inappropriate.
65	Newcastle	Full	167	l 2	'Pharmacological management of blood glucose	Thank you for your feedback. CG66 replaced all

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9	Hospitals NHS Trust			section 8.4.1.2	levels was originally covered as part of 2 CG66 and CG87.' This is wrong - it was 'originally' covered in all previous NICE guidelines for type 2 diabetes, from the NICE-inherited guideline (published 2002) onwards.	previous versions of the type 2 diabetes guideline and as CG87 only partially updated CG66, both documents have been referred to in the 2015 update.
639	Newcastle Hospitals NHS Trust	Full	21	rec 54	This discriminates between care teams and should be unacceptable. There are no special technical issues here for people using the individual agents already.	Thank you for your comment.
641	Newcastle Hospitals NHS Trust	Full	22	rec 64	Should modified release metformin be stopped? Many people will be using it because they tolerate it but did not tolerate IR metformin? This appears to be the implication. To lose the vascular protection as a result would be extremely bad clinical practice, not even defensible in law. It appears to be unjustifiable discrimination against those who find it helpful when the IR preparation causes GI problems.	Thank you for your feedback. The recommendation has been amended to: "*When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.*"
636	Newcastle Hospitals NHS Trust	Full	254 255	l 15, rec 46 l 31, rec 54	While in RCTs all comers are taken, in clinical practice in continuing ambulatory care people with diabetes may deteriorate to higher HbA_{1c} despite good self-care behaviours and current therapy. These people account for the population that in most RCTs show that once above 8.0 % HbA_{1c} (64 mmol/mol) adding another oral agent stands little chance of getting adequate control (<7.0 %). It is unclear this has been considered by the GDG, ie that in some circumstances insulin should be started earlier rather than allowing vascular rot, or that combinations of agents might be introduced	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and

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					together or in rapid succession. Rec 46 which deals with only symptomatic hyperglycaemia is not adequate to deal with this, an important failing.	emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
637	Newcastle Hospitals NHS Trust	Full	254 and elsewhere	l, rec 46 et seq	CG66/87 noted similarly that there may be occasions when starting initial therapy that metformin be combined with sulfonylureas or insulin (both of which have a much fasting onset of effect than metformin or thiazolidinediones (ADOPT). This now seems missing. It is a real need and common dilemma in practice.	**Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In**

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						addition, recommendation 1.6.18 (NICE version) provides guidance on starting a sulfonylurea or insulin in symptomatically hyperglycaemic individuals.
630	Newcastle Hospitals NHS Trust	Full	255	rec 50-54 and preceding text in this section	The basis for recommending one agent over another amongst the generic priced drugs (sulfonylureas, repaglinide, pioglitazone) other than metformin appears perverse on a number of accounts, and flawed on others: 1. The network analysis and systematic reviews confirm what is generally known and accepted wisdom namely that at 12 months glucose-lowering efficacy is broadly similar (after early advantage for the two insulin secretagogues lost by 8 months), there is hypoglycaemia with the insulin secretagogues (SU/repaglinide) but not pioglitazone, and that weight gain occurs with all three agents. Notably where similar, there are no statistically significant differences between agents (appendix J). It is then perverse and misleading to enter different central estimates in to the economic model, and then rely on the small differences in QALYs (highly uncertain) in decision making. Most of the QALY differences in Table 64 are probably not real, and many of the costs essentially the same. 2. Care seems not to have been taken with long-term modelling of weight gain and glucose control. Good data is only available from the ADOPT study but confirms that sulfonylurea weight gain is strictly time limited (there are	Thank you for your feedback. 1. Differences in lifetime discounted QALYs were driven by weight; differences in lifetime discounted costs were driven by treatment costs (appendix F 4.1). These differences were derived from a fully probabilistic model, meaning differences (whilst small) were sustained over many model runs. However, the guideline development group felt a hierarchy of options was not supportable. 2. The health economic model had annual cycles and was not structured to consider shorter term changes in treatment effects. All type 2 diabetes health economic models use annual cycles. Other analyses have assumed treatment effect data from less than 12 months could be applied at 12 months, this analysis chose to only use 12 month data. This was noted as a limitation (appendix F 5.2.1). 3. Long-term risks associated with different treatment options were assessed in a separate review question. Whilst it was not possible to incorporate these risks within the health economic modelling, it is of note that no type 2

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					reasons for this) while that of thiazolidinediones (in ADOPT the class is represented by rosiglitazone) is not. Repaglinide in the absence of evidence and working on the same islet B-cell ion channel mechanism as the sulfonylureas should be modelled similarly. Glucose control however deteriorated linearly from 8-12 months with sulfonylureas (again the same would be expected of glinides), but to only a small extent with the thiazolidinedione, consistent with other evidence for pioglitazone. Again this seems not to have been modelled. Although ADOPT was monotherapy the glucose control curves were identical in the add-on RECORD study over 5 years (data can be provided on request). 3. Inadequate weight seems to have been placed on long-term safety data. Sulfonylureas were a large part of the cohort which in UKPDS showed with time a reduction in MI and even all cause mortality, did better than even metformin for myocardial ischaemia (FDA website) in the ADOPT study), and did equivalently to metformin and rosiglitazone for CV vascularizations in RECORD (a study reviewed in unprecedented depth by the FDA and not found wanting). These studies gained a mass of safety data (including cancer), added to by the large ADVANCE study, in which gliclazide was the major intervention (amongst others). There is not such data for repaglinide (a novel chemical entity) and somewhat limited post-	diabetes health economic models currently incorporate the long-term risks associated with different treatment options. The guideline development group considered long-term risk evidence alongside clinical and cost effectiveness and noted the need to consider MHRA safety advice when discussing the risks and benefits of treatment options with people with type 2 diabetes. 4 and 5. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The guideline development

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					marketing experience. Pioglitazone is probably good in regard of vascular disease (PROactive), but heart failure is a real problem as are fractures (extra 1 per 100 women per year), and the bladder cancer issue is unresolved. It then seems perverse to recommend repaglinide with no statistically significant advantages as above before sulfonylureas, and indeed pioglitazone before sulfonylureas. While NICE does not like opinion (but Appraisal Committees always seek it) this is not just personal comment – the Editor's Forum of the global leading clinical journal published similar conclusions in 2014, and this for a drug class which no one promotes. 4. The GDG need to ask themselves why repaglinide is so little prescribed, and pioglitazone is now uncommonly initiated in contrast to the sulfonylureas which have only lost market slowly as the subject of heavy competitive marketing by the DPP-4i manufacturers. Repaglinide despite heavy promotion never took off because it is difficult to use (tds, blister packs are 90), extra self-monitoring was needed to adjust the individual doses, the midday dose was disliked by patients (probably with low adherence), with no advantages over gliclazide/glimepiride. Pioglitazone is probably a good agent, but the continuing weight gain is hated, the oedema and heart failure are not uncommon, distal fractures are a problem (see above), and explaining to	group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

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					patients (and asking after other risk factors) that bladder cancer is an issue is not easy and costly in time. NICE and the GDG needs to ask themselves whether the change from CG66/87 to recommendations to use agents which clinicians do not generally prescribe is going to promote good clinical care, or rather lead to the new guidelines being widely ignored. 5. A sensible conclusion would be that the generic agents for second line use (add on to metformin or replacement to metformin if not tolerated) or first line (metformin intolerance) should simply be left as alternatives to be chosen by personal individual characteristics and preferences.	
631	Newcastle Hospitals NHS Trust	Full	255	rec 52, l 12	The suggestion that the DPP-4 inhibitors should be considered alongside generic agents second line (without specific contraindications to these) needs be questioned. It is true that hypoglycaemia is not a problem with these drugs, nor is weight gain, but overall the glucose-lowering efficacy appears lower, and the cost is much higher than sulfonylureas. My reading of the economic output is that they are dominated by the generics, not because of the QALY differences which are small, but the lifetime costs. However it is true that for sitagliptin the exposure in the US means that they are known to be safe, although caution should be applied until the TECOS results are	Thank you for your feedback. The recommendations have been amended to encourage the consideration of benefits and risks of each treatment option. Long-term drug safety was considered in a separate review question, with a search date cut off of June 2014. Any studies published after this date could not be included in this update.

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					available this June (a question over heart failure remains from the saxagliptin study SAVOR). Indeed failure to incorporate TECOS if the findings are novel may mean the guidelines in this section are outdated at the time of their publication.	
632	Newcastle Hospitals NHS Trust	Full	256 also p 14, 15 (algorithms)	l 20	A further problem of guideline relevance is time proofing (echoes of CG66) but also is important to practising clinicians. It is difficult to believe that NICE should expect HCPs to consult different NICE documents when taking one decision. The guidance for dapagliflozin and canagliflozin is public domain, and while the evidence reviews and economic analyses are not easy to concatenate, the conclusions are. It is not difficult to summarize the guidance – the drugs can be used where DPP-4i's would be considered, though I would make a plea that the safety data as yet available for this class is thin.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
635	Newcastle Hospitals NHS Trust	Full	257	l 1, rec 60	As noted in the previous point the GLP-1 receptor agonist market is expanding. But the review of currently available GLP-1RAs appears weak. Exenatide IR and liraglutide have very different side effect profiles, and administration requirements, and different glucose lowering, while similar effects on blood pressure and body weight. This is emphasized by exenatide MR (seemingly missed in consideration) which proved better than exenatide IR in glucose-lowering but failed non-inferiority to liraglutide, although is even better for GI side effects. It	Thank you for your feedback. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics including exenatide modified release were included at the cut off search date of June 2014. Exenatide IR and MR were considered separately in the analyses.

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					does not seem that all these issues have been adequately addressed by the GDG in their consideration, or even in the HE analysis. And as noted above exenatide MR is now reformulated, and two new weekly agents will shortly be marketed in the UK, so perhaps this whole class needs re-evaluation. Least acquisition cost as in the recommendation is not properly justified in the draft documents.	
642	Newcastle Hospitals NHS Trust	Full	258	l 14, rec 65	'the person cannot use the device to inject NPH insulin.' Not English	Thank you for your feedback.
643	Newcastle Hospitals NHS Trust	Full	258	l 36, rec 67	An alternative here is a GLP-1RA; this has advantages in terms of weight gain and hypoglycaemia (all evidence-based), and requires much less SMPG and supervision, but is perhaps more expensive than adding meal-time insulin in acquisition cost but not treatment cost. Useful if hypoglycaemia or body weight gain a barrier to further insulin optimization.	Thank you for your feedback. The recommendations made on GLP-1 mimetics are based on the systematic evaluation of available relevant clinical and health economic evidence.
644	Newcastle Hospitals NHS Trust	Full	271	l 33, rec 72	Perhaps referral should also occur if gastroparesis appears to be leading to sub-optimal glucose control – a common scenario. We missed that in CG66.	Thank you for your feedback. This section of the type 2 diabetes guideline was not prioritised for update following a stakeholder workshop and stakeholder consultation at the scoping stage. It was considered by the type 1 diabetes guideline and both guideline development committees agreed that the management of gastroparesis was likely to be similar between people with type 1 and type 2 diabetes. Therefore, 2 recommendations on the treatment of gastroparesis from the type 1 diabetes guideline

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						have been adopted in the type 2 diabetes guideline. In the recommendations, domperidone is recognised as having the strongest evidence for effectiveness but that it should only be used in exceptional circumstances when metoclopramide or erythromycin have not been effective, based on the recent safety issues highlighted by the MHRA. The type 2 diabetes guideline retains the recommendation to refer people with gastroparesis in circumstances where the differential diagnosis is in doubt or persistent or severe vomiting occurs.
645	Newcastle Hospitals NHS Trust	Full	290	l 26, rec 93:	The change in wording to 'large sudden' drop in visual acuity is not satisfactory, indeed dangerous wording. As VA is usually only measured yearly 'sudden' has no meaning. A confirmed drop of even one line can indicate development of macula oedema. Of course VA does fluctuate with a CV of one line in some people (partly with glucose control but also other eye problems and measurement conditions), so the key discriminator is confirmation (past measurements will be serial, current can be repeated), not 'large'. Large can be too late to be reversible. This rec is bad medical practice.	Thank for your comment. The advice of the diabetic eye screening programme was sought on these recommendations which have not been updated by an evidence review. The comment has been highlighted to the diabetic eye screening programme.
648	Newcastle Hospitals NHS Trust	Full	32 section 2.3	l 26-27	It might be worth pointing out that the guideline does not apply to common forms of diabetes often confused with type 2 diabetes, namely secondary diabetes (endocrinological or pancreatic).	Thank you for your feedback. The text has been amended.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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646	Newcastle Hospitals NHS Trust	Full	32 section 2.2	l 4-6	This statement an oxymoron. Incidence is number of people per thousand developing diabetes per year, the figure of 1 in 20 is prevalence, and anyway merely an approximate restatement of the previous paragraph.	Thank you for your feedback. The text has been amended.
647	Newcastle Hospitals NHS Trust	Full	32 section 2.2	l 6-8	This sentence implies that the majority of people in certain ethnic groups have type 2 diabetes diagnosed before age 40 years. Simply wrong. In the next sentence 'age groups' are referred to without definition – 'at any age'. The general standard of English seems to have slipped from CG66/87 in 2008-9.	Thank you for your feedback. The text has been amended.
650	Newcastle Hospitals NHS Trust	Full	33 section 2.5,	l 10-12	What is the relevance of this statement about children under 16 yr to a guideline specifically addressing those over 17 years?	Thank you for your comment. This is standard NICE template text which appears in all guidelines.
649	Newcastle Hospitals NHS Trust	Full	33 section 2.5	l 1-2	Is this true ('younger adults')? Perhaps the NICE rejected most of the evidence from the RCTs, but typical mean age for these is late 50's or more (see indeed Table 45). Even to some senior citizens this is middle-age – 'younger adults' would usually imply age 18-35 years. It is true that older RCTs did tend to have cut-offs of age 75 yr (now no longer true) so the 'elderly' were excluded, but this does not justify the misleading term 'younger adults'.	Thank you for your feedback. The text has been amended.
651	Newcastle Hospitals NHS Trust	Full	35 section	l 15-16	This is not true for people on insulin therapy as the guideline recognizes elsewhere, and indeed recommends. Did any diabetes health professional review this text? It appears there	Thank you for your feedback. The text has been amended.

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			3.2.1		have been procedural failures here.	
652	Newcastle Hospitals NHS Trust	Full	35 section 3.2.4	l 29-33	This is an extraordinary statement, and is fundamentally flawed. Firstly when considering individual medication (or class indications) specific adverse events are of course important. Examples would be lactic acidosis for metformin, and fractures, heart failure, fluid retention and bladder cancer for pioglitazone. More generally the evidence from questionnaire studies is that the comparative adverse outcomes which matter to people with diabetes are hypoglycaemia and weight gain – reported in most studies, and accounting for the separate approach in the next two sections. The GDG, searches, and HE analysis did not ignore these – see what follows.	Thank you for your feedback. As indicated in your comment, hypoglycaemia and weight gain are important outcomes for patients, which is why these outcomes were reported separately. Lines 29-33 refer to other adverse events and comparing these across different drugs/classes and studies.
654	Newcastle Hospitals NHS Trust	Full Also appendix J	37 section 3.4.1:	l 32	My comment does not relate to data imputation but an issue related to change from baseline addressed in this section. It is well documented in glucose-lowering trials that the principal determinant of change in HbA1c is baseline HbA1c and not the therapy of study. I cannot see that correction has been made for this – without it the comparative analyses would usually be regarded as flawed. However I would accept that use of only differences from control studies (placebo or active) would partially mitigate the effect..	Thank you for your feedback. As outlined in section 3.6.2.9 of the guideline, use of baseline HbA1c as a covariate was explored. It was not used in the network meta-analyses to produce relative treatment effects, but was used in the health economic modelling to produce absolute treatment effects (appendix F 3.5.1).
655	Newcastle Hospitals NHS Trust	Full	38	l 14-15:	'When events are likely to occur to a person more than once (for example, hypoglycaemic events), it is preferable to use count or rate	Thank you for your feedback. The implications of hypoglycaemic events, with regard to both impact on the patient's quality of life and

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			3.4.2		data.' This is not correct for hypoglycaemia in particular. Event rate and proportion affected can both be important numbers for clinical practice, although often both are not reported in oral agent (usually proportion) as opposed to insulin studies. The problem is that the distribution curve of hypoglycaemia is a decay curve, most events occurring in very few people. Obviously if most events are occurring in <2 % of the population then rate (events/person-year) is a highly misleading statistic not applicable to 98% (and easily clinically managed by changing therapy). Here people/proportion affected (say the 30% of people have at least one event) is more clinically important – one fall in an old lady or collapse when shopping is the risk that matters. People/proportion affected also gives prediction of a much bigger health care burden, in practice is a more informative for oral agents, and more statistically powerful even for insulin in type 2 diabetes (because multiple events in one person are correctly not treated as independent by the usual C-M-H analysis) (not true of type 1 diabetes). I note that any meta-analysis or network analysis that does not take account of hypoglycaemia event distribution within each study is invalid (not true of number or people affected/proportion data). This comment applies to the usual definitions of hypoglycaemia (confirmed; documented	healthcare resource use and costs, will be critically dependent on the number of events each person experiences. The guideline development group (GDG) and developers considered it unacceptable to discard this information and focus, instead, on the probability that individuals would experience 1 or more event. The kind of significant event cited in the feedback is more likely to happen if patients experience multiple episodes, and this should not be ignored. From a health economic modelling perspective, even if probability of event was used as the input of interest, it would be necessary to estimate number of events separately, and this would be mathematically equivalent to – though less robustly parameterised than – relying on rate data. The point that experience of hypoglycaemia may be an impetus for switching therapy is a potentially important one. The HE model includes 2 causes of treatment discontinuation – inadequate control of HbA1c and withdrawal due to AEs. We assume that, in a good number of the cases reported in trials, the latter type of discontinuation reflects experience of hypoglycaemia. If so, this eventuality will be adequately reflected in the model. However, if it is the case that people in trials will tolerate a higher incidence of hypoglycaemia than would be seen in practice, the model will overestimate the amount of time people spend on treatments

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					symptomatic). For the hospitalizations it is perhaps not true, and for 'severe' (requiring third party assistance) it has less impact.	that are associated with higher incidence of hypoglycaemia and it will overestimate the costs and quality of life implications for those treatments.
666	Newcastle Hospitals NHS Trust	Appendix F	82	3.8	The newly introduced GLP-1 agents albiglutide and dulaglutide do not seem to be included, perhaps understandably, nor the change in exenatide MR device to the Bydureon Pen. Indeed it seems 'exenatide' is often terminologically used for exenatide IR in this section (incorrectly), and exenatide MR, on the market for some time ignored. In Table 6 In Table 42, page 169, the exenatide MR dose is tellingly missing.	Thank you for your feedback. Included treatment options were limited to those for whom evidence was found. Exenatide modified-release was not included in the health economic modelling as data were not available for all 4 outcomes.
663	Newcastle Hospitals NHS Trust	Appendix F	86	Table 65	There is a suspicion that the repaglinide unit mg drug cost here is wrong. Since I do not have access to the specific NHS Drug Tariff versions used I cannot be specific. However the drug is given tds ('with main meals', and supplied in blisters of 90) so the 4 mg or 3.96 mg assumed is a combination of use of 0.5 mg tds, 1 mg tds, and 2 mg tds. Both 0.5 mg and 1 mg are much more expensive per mg than 2 mg per mg dose, so the mix is critical to cost. 2x2 mg will severely underestimate acquisition cost. 1 mg tds will dominate proportionately, but the exact mix will have to be guessed. Perhaps 0.67 using 3x1 mg, 0.25 using 3x2 mg and the rest 3x0.5 mg?	Thank you for your feedback. The methods used to derive unit costs are detailed in appendix F section 3.8.3 and were agreed by the guideline development group. In line with your suggestion, it would have been possible to adopt an alternative approach that aimed to reflect currently prevailing – though not necessarily optimal – prescribing patterns. This would have had implications not only for the cost of repaglinide, but for all treatment options consideredHowever, the view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence

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						available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
664	Newcastle Hospitals NHS Trust	Appendix F	86	Table 65	Although not likely to have a large effect the assumptions of SMPG monitoring use with insulin and even injection number (needle use) appear wrong in this table. For example basal insulin with glargine is mainly titrated on 1 SMPG per day, somewhat higher for detemir (often used bd), and around double for NPH which is usually given twice daily and gives more hypoglycaemia. Conventional premixes require more than NPH for the same reason. On injection number IDegAsp will often be given (perhaps usually) twice a day, and was so in some of the studies evidenced.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
665	Newcastle Hospitals NHS Trust	Appendix F	86	Table 65	By around 4-5 years after starting insulin around 50% will be using a basal + meal-time multiple injection insulin regimen – this does not appear here at all. See CREDIT study in DRCP for evolution of regimens in developed nations.	Thank you for your feedback. No clinical evidence was included covering basal + meal time multiple injection regimes (see full guideline 8.4.16). Therefore such treatment options were not included in the health economic modelling.
660	Newcastle Hospitals NHS Trust	Appendix F	88	Table 65	There appears to be major error in SMPG assumptions. Sulfonylureas are assumed to require 3/week and repaglinide none. Both are insulin secretagogues working on the same	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the

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					cellular mechanism and both cause hypoglycaemia. Further the tds administration of repaglinide usually means more strips are used than for gliclazide (the main SU you assume). Since SMPG costs exceed drug acquisition costs this is likely to have significant effects on treatment costs and differences between these insulin secretagogues. Indeed this more than accounts for the difference between SU and repaglinide in Table 66 (Annual treatment costs) – SU should be lower cost	guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
661	Newcastle Hospitals NHS Trust	Appendix F	88	Table 65	There appears to be major error in SMPG assumptions. Pioglitazone does not cause hypoglycaemia and used as monotherapy does not per se require SMPG. Your SMPG recommendations seem only to be for those at risk. This problem extends to metformin-pioglitazone (again does not cause hypoglycaemia), and the GLP-1RA agents in combination with metformin, none of which carries a hypoglycaemia risk in this situation.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
662	Newcastle Hospitals NHS Trust	Appendix F	88	Table 65	The assumed rates of SMPG use with sulfonylureas (and indeed with repaglinide) differ according to use in combination or otherwise.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called

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					Essentially combination of any agent with an insulin secretagogue enhances the rate of hypoglycaemia (many many studies). A reasonable assumption might be that your SMPG rate of 3/week is correct for combination therapy where one agent or more is a sulfonylurea, but for monotherapy rates (except in cases of occupational risk – low proportion) would be better modelled at 1/week. For repaglinide see below, comment 8, sub-point 4, which deals with the higher rate of SMPG use with this drug.	for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
656	Newcastle Hospitals NHS Trust	Full	98	l 28 8.1.1 .2	This is a very odd statement about rosiglitazone. As a result of the RECORD study re-examination by the FDA the drug has been returned without restriction to the US market, and the US label (SmPC equivalent) only warns about heart failure, as class effect. In Europe it remains suspended, but because the manufacturer has not been motivated to ask for review of the issues. It is possible the GDG opinion, always naive, predated the FDA/Duke reviews. The rosi papers have useful comparative information (eg sulfonylurea vs metformin) anyway, and similarly network information independent of rosiglitazone, so it anyway appears to have been illogical and perverse to exclude them. There is some very strong data here.	Thank you for your feedback. Rosiglitazone comparisons were excluded. However, where studies included multiple arms with comparisons of interest for example, metformin versus placebo, such data were extracted.
63	Newcastle	Full	Gene	gene	Unlike the SGLT2i's (previous point) the	Thank you for your comment. NICE cannot

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

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4	Hospitals NHS Trust		ral	ral comment	guideline also has the problem that several other newly marketed products are appearing/have appeared in 2015. Thus the new formulation of exenatide MR (pen), albiglutide, dulaglutide, biosimilar insulin glargine (Lilly), other SGLT2's. This commentator would accept these probably cannot make the current version of the guideline, but it does suggest a rapid update will be required within 12 months. Indeed given the pace of change in glucose-lowering medications should this not be a living guideline with yearly updates?	provide comment on biosimilars within the guidance until such time they become available. Please see the NICE position statement on biosimilars. However, the suggestion has been logged and will be considered for update at an earlier juncture than usual.
638	Newcastle Hospitals NHS Trust	Full	General	section 8.4	Missing Issue CG66/87 suggested a considering trial of metformin MR if metformin IR is not tolerated. This appears to have disappeared in favour of starting repaglinide or other agents. In glucose-lowering HE terms this might appear correct, but metformin has the strongest evidence base for vascular protection, while repaglinide has none – ie an HE analysis for repaglinide for CV protection does not get past the starting post. It is true that the evidence base for GI side effects on metformin MR vs IR is not strong (but how would you do the placebo controlled trial in the intolerant?) but the cost of a trial of therapy in the individual is trivial (?£10) as it will be stopped again if intolerance recurs, while if it can be continued the outcome gain as per UKPDS would be large.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
48	Newcastle	Full	123	l 42,	This discrimination in regard of the elderly is	Thank you for your feedback. Many stakeholders

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7	University			rec 40	unacceptable. Indeed later the document notes (p 122 8.1.3) 'The GDG thought that, when agreeing target values with adults with type 2 diabetes, it is more important to consider the nature of the individual's current medical condition – that is, diabetes, its complications and any other comorbidities – rather than age alone.' Quite! There are rather a lot of unnecessary references to older people in this document. Plenty of people of younger age are similarly vulnerable.	have highlighted the increased risk of adverse effects (such as hypoglycaemia) of tight glycaemic control particularly in older or frail individuals. The guideline development group has also highlighted other cirumstances when HbA1c targets should be relaxed (see Recommendation 1.6.9 in NICE version).
506	Newcastle University	Full	124	l 1 et seq section 8.2 (whole)	This is most odd, as essentially the question is answered and dealt with already in 8.1. Furthermore terminological bias is introduced here, as much of what is called 'intensive' is now usual practice as section 8.1 recognizes, and most of what is meant by 'conventional' is better termed 'historic'. It would be better to integrate this section with 8.1 as they address the same question, allowing the recommendations of 8.1 to stand. Often the difference in glucose control within the studies cited is only around 1.0 % (11 mmol/mol) HbA_{1c}, and the meta-analyses wrongly concatenate studies of people in very different circumstances (UKPDS, newly diagnosed, long study duration; DIGAMI, post-MI, and short study duration; UGDP, historic therapy with failed randomization; etc). Basically the evidence analysis here is very poor quality indeed, and the meta-analysis would not be publishable. A more intelligent Bayesian	Thank you for your feedback. Although it is recognised that the collective evidence informed the overall recommendations, because sections 8.1 and 8.2 included different types of studies, it was necessary to undertake these reviews separately. The guideline development group noted the lack of consistency in the definition of intensive and conventional targets and that this differed between included studies which may have changed over time. Due to the potential for confusion by the indeterminate nature of intensive and conventional terminology, the group agreed that HbA1c target values should be provided without any attempt to dichotomise into either group. Therefore, all the recommendations for target values are included in Section 8.1.4 in the full guideline. The analysis for Section 8.2 is derived from a Cochrane systematic review. Overall, the levels of heterogeneity were considered to be acceptable (see forest plots in

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					approach using some of the modern studies excluded would have been more sensible, though not easy and not previously attempted.	Appendix D). However, where heterogeneity was considered to be serious or very serious, the quality was downgraded in the GRADE assessment.
480	Newcastle University	Full	14 , 15	algorithms	These algorithms are even more complicated and less easy to follow than those of CG66/87. The minds of the people who draw these clearly work in different ways from most health care professionals. Have a look at the simpler format used by the International Diabetes Federation and Chinese Diabetes Society. They are comprehensible unlike these diagrams.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
507	Newcastle University	Full	166	l 23 and other section 8.4	There is an important terminological problem with this section. It refers to stepped therapy as 'intensification'. There is nothing intensive about taking two glucose lowering therapies once HbA_{1c} has deteriorated to above 53 mmol/mol, any more than taking two anti-hypertensives if your BP is above 140 mmHg systolic. The use of this term gives the wrong educational message. Intensification would be adding another agent to someone already in adequate control. To describe appropriate prescription of one drug as an intensive action is misleading.	Thank you for your feedback. The guideline development group gave much consideration on the terminology used. Options such as "first/second line", "phase" or based on numbered agents (mono, dual) were considered inappropriate.
485	Newcastle University	Full	166	section 8.4	CG66/87 suggested a considering trial of metformin MR if metformin IR is not tolerated. This appears to have disappeared in favour of	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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				missing issue	starting repaglinide or other agents. In glucose-lowering HE terms this might appear correct, but metformin has the strongest evidence base for vascular protection, while repaglinide has none – ie an HE analysis for repaglinide for CV protection does not get past the starting post. It is true that the evidence base for GI side effects on metformin MR vs IR is not strong (but how would you do the placebo controlled trial in the intolerant?) but the cost of a trial of therapy in the individual is trivial (?£10) as it will be stopped again if intolerance recurs, while if it can be continued the outcome gain as per UKPDS would be large.	pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
508	Newcastle University	Full	167	l 2 section 8.4.1.2	'Pharmacological management of blood glucose levels was originally covered as part of 2 CG66 and CG87.' This is wrong - it was 'originally' covered in all previous NICE guidelines for type 2 diabetes, from the NICE-inherited guideline (published 2002) onwards.	Thank you for your feedback. CG66 replaced all previous versions of the type 2 diabetes guideline and as CG87 only partially updated CG66, both documents have been referred to in the 2015 update.
486	Newcastle University	Full	21	rec 54	This discriminates between care teams and should be unacceptable. There are no special technical issues here for people using the individual agents already.	Thank you for your comment.
488	Newcastle University	Full	22	rec 64	Should modified release metformin be stopped? Many people will be using it because they tolerate it but did not tolerate IR metformin? This appears to be the implication. To lose the vascular protection as a result would be extremely bad clinical practice, not even defensible in law. It appears to be unjustifiable	Thank you for your feedback. The recommendation has been amended to: "*When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.*"

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					discrimination against those who find it helpful when the IR preparation causes GI problems.	
483	Newcastle University	Full	254 255	l 15, rec 46 l 31, rec 54	While in RCTs all comers are taken, in clinical practice in continuing ambulatory care people with diabetes may deteriorate to higher HbA_{1c} despite good self-care behaviours and current therapy. These people account for the population that in most RCTs show that once above 8.0 % HbA_{1c} (64 mmol/mol) adding another oral agent stands little chance of getting adequate control (<7.0 %). It is unclear this has been considered by the GDG, ie that in some circumstances insulin should be started earlier rather than allowing vascular rot, or that combinations of agents might be introduced together or in rapid succession. Rec 46 which deals with only symptomatic hyperglycaemia is not adequate to deal with this, an important failing.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
484	Newcastle University	Full	254 and elsewhere	l, rec 46 et seq	CG66/87 noted similarly that there may be occasions when starting initial therapy that metformin be combined with sulfonylureas or insulin (both of which have a much fasting onset of effect than metformin or thiazolidinediones (ADOPT). This now seems missing. It is a real need and common dilemma in practice.	**Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The**

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						recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, recommendation 1.6.18 (NICE version) provides guidance on starting a sulfonylurea or insulin in symptomatically hyperglycaemic individuals.
477	Newcastle University	Full	255	rec 50-54 and preceding text in this section	The basis for recommending one agent over another amongst the generic priced drugs (sulfonylureas, repaglinide, pioglitazone) other than metformin appears perverse on a number of accounts, and flawed on others: 1. The network analysis and systematic reviews confirm what is generally known and accepted wisdom namely that at 12 months glucose-lowering efficacy is broadly similar (after early advantage for the two insulin secretagogues lost by 8 months), there is hypoglycaemia with the insulin secretagogues (SU/repaglinide) but not	Thank you for your feedback. 1. Differences in lifetime discounted QALYs were driven by weight; differences in lifetime discounted costs were driven by treatment costs (appendix F 4.1). These differences were derived from a fully probabilistic model, meaning differences (whilst small) were sustained over many model runs. However, the guideline development group felt a hierarchy of options was not supportable.

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					pioglitazone, and that weight gain occurs with all three agents. Notably where similar, there are no statistically significant differences between agents (appendix J). It is then perverse and misleading to enter different central estimates in to the economic model, and then rely on the small differences in QALYs (highly uncertain) in decision making. Most of the QALY differences in Table 64 are probably not real, and many of the costs essentially the same. 2. Care seems not to have been taken with long-term modelling of weight gain and glucose control. Good data is only available from the ADOPT study but confirms that sulfonylurea weight gain is strictly time limited (there are reasons for this) while that of thiazolidinediones (in ADOPT the class is represented by rosiglitazone) is not. Repaglinide in the absence of evidence and working on the same islet B-cell ion channel mechanism as the sulfonylureas should be modelled similarly. Glucose control however deteriorated linearly from 8-12 months with sulfonylureas (again the same would be expected of glinides), but to only a small extent with the thiazolidinedione, consistent with other evidence for pioglitazone. Again this seems not to have been modelled. Although ADOPT was monotherapy the glucose control curves were identical in the add-on RECORD study over 5 years (data can be provided on request). 3. Inadequate weight seems to have been	2. The health economic model had annual cycles and was not structured to consider shorter term changes in treatment effects. All type 2 diabetes health economic models use annual cycles. Other analyses have assumed treatment effect data from less than 12 months could be applied at 12 months, this analysis chose to only use 12 month data. This was noted as a limitation (appendix F 5.2.1). 3. Long-term risks associated with different treatment options were assessed in a separate review question. Whilst it was not possible to incorporate these risks within the health economic modelling, it is of note that no type 2 diabetes health economic models currently incorporate the long-term risks associated with different treatment options. The guideline development group considered long-term risk evidence alongside clinical and cost effectiveness and noted the need to consider MHRA safety advice when discussing the risks and benefits of treatment options with people with type 2 diabetes. 4 and 5. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations

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					placed on long-term safety data. Sulfonylureas were a large part of the cohort which in UKPDS showed with time a reduction in MI and even all cause mortality, did better than even metformin for myocardial ischaemia (FDA website) in the ADOPT study), and did equivalently to metformin and rosiglitazone for CV vascularizations in RECORD (a study reviewed in unprecedented depth by the FDA and not found wanting). These studies gained a mass of safety data (including cancer), added to by the large ADVANCE study, in which gliclazide was the major intervention (amongst others). There is not such data for repaglinide (a novel chemical entity) and somewhat limited post-marketing experience. Pioglitazone is probably good in regard of vascular disease (PROactive), but heart failure is a real problem as are fractures (extra 1 per 100 women per year), and the bladder cancer issue is unresolved. It then seems perverse to recommend repaglinide with no statistically significant advantages as above before sulfonylureas, and indeed pioglitazone before sulfonylureas. While NICE does not like opinion (but Appraisal Committees always seek it) this is not just personal comment – the Editor's Forum of the global leading clinical journal published similar conclusions in 2014, and this for a drug class which no one promotes. 4. The GDG need to ask themselves why repaglinide is so little prescribed, and	and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. In addition, a footnote on MHRA guidance on safety alerts for

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					pioglitazone is now uncommonly initiated in contrast to the sulfonylureas which have only lost market slowly as the subject of heavy competitive marketing by the DPP-4i manufacturers. Repaglinide despite heavy promotion never took off because it is difficult to use (tds, blister packs are 90), considerable extra self-monitoring was needed to adjust the individual doses, the midday dose was disliked by patients (probably with low adherence), with no advantages over gliclazide/glimepiride. Pioglitazone is probably a good agent, but the continuing weight gain is hated, the oedema and heart failure are not uncommon, distal fractures are a problem (see above), and explaining to patients (and asking after other risk factors) that bladder cancer is an issue is not easy and costly in time. NICE and the GDG needs to ask themselves whether the change from CG66/87 to recommendations to use agents which clinicians do not generally prescribe is going to promote good clinical care, or rather lead to the new guidelines being widely ignored. 5. A sensible conclusion would be that the generic agents for second line use (add on to metformin or replacement to metformin if not tolerated) or first line (metformin intolerance) should simply be left as alternatives to be chosen by personal individual characteristics and preferences.	pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

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478	Newcastle University	Full	255	rec 52, l 12	The suggestion that the DPP-4 inhibitors should be considered alongside generic agents second line (without specific contraindications to these) needs be questioned. It is true that hypoglycaemia is not a problem with these drugs, nor is weight gain, but overall the glucose-lowering efficacy appears lower, and the cost is much higher than sulfonylureas. My reading of the economic output is that they are dominated by the generics, not because of the QALY differences which are small, but the lifetime costs. However it is true that for sitagliptin the exposure in the US means that they are known to be safe, although caution should be applied until the TECOS results are available this June (a question over heart failure remains from the saxagliptin study SAVOR). Indeed failure to incorporate TECOS if the findings are novel may mean the guidelines in this section are outdated at the time of their publication.	Thank you for your feedback. The recommendations have been amended to encourage the consideration of benefits and risks of each treatment option. Long-term drug safety was considered in a separate review question, with a search date cut off of June 2014. Any studies published after this date could not be included in this update.
479	Newcastle University	Full	256 also p 14, 15 (algorithms)	l 20	A further problem of guideline relevance is time proofing (echoes of CG66) but also is important to practising clinicians. It is difficult to believe that NICE should expect HCPs to consult different NICE documents when taking one decision. The guidance for dapagliflozin and canagliflozin is public domain, and while the evidence reviews and economic analyses are not easy to concatenate, the conclusions are. It is not difficult to summarize the guidance – the	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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					drugs can be used where DPP-4i's would be considered, though I would make a plea that the safety data as yet available for this class is thin.	TA guidance.
482	Newcastle University	Full	257	l 1, rec 60	As noted in the previous point the GLP-1 receptor agonist market is expanding. But the review of currently available GLP-1RAs appears weak. Exenatide IR and liraglutide have very different side effect profiles, and administration requirements, and different glucose lowering, while similar effects on blood pressure and body weight. This is emphasized by exenatide MR (seemingly missed in consideration) which proved better than exenatide IR in glucose-lowering but failed non-inferiority to liraglutide, although is even better for GI side effects. It does not seem that all these issues have been adequately addressed by the GDG in their consideration, or even in the HE analysis. And as noted above exenatide MR is now reformulated, and two new weekly agents will shortly be marketed in the UK, so perhaps this whole class needs re-evaluation. Least acquisition cost as in the recommendation is not properly justified in the draft documents.	Thank you for your feedback. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics including exenatide modified release were included at the cut off search date of June 2014. Exenatide IR and MR were considered separately in the analyses.
489	Newcastle University	Full	258	l 14, rec 65	'the person cannot use the device to inject NPH insulin.' Not English	Thank you for your feedback.
490	Newcastle University	Full	258	l 36, rec 67	An alternative here is a GLP-1RA; this has advantages in terms of weight gain and hypoglycaemia (all evidence-based), and requires much less SMPG and supervision, but	Thank you for your feedback. The recommendations made on GLP-1 mimetics are based on the systematic evaluation of available relevant clinical and health economic evidence.

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					is perhaps more expensive than adding meal-time insulin in acquisition cost but not treatment cost. Useful if hypoglycaemia or body weight gain a barrier to further insulin optimization.	
491	Newcastle University	Full	271	l 33, rec 72	Perhaps referral should also occur if gastroparesis appears to be leading to sub-optimal glucose control – a common scenario. We missed that in CG66.	Thank you for your feedback. This section of the type 2 diabetes guideline was not prioritised for update following a stakeholder workshop and stakeholder consultation at the scoping stage. It was considered by the type 1 diabetes guideline and both guideline development committees agreed that the management of gastroparesis was likely to be similar between people with type 1 and type 2 diabetes. Therefore, 2 recommendations on the treatment of gastroparesis from the tpe 1 diabetes guideline have been adopted in the type 2 diabetes guideline. In the recommendations, domperidone is recognised as having the strongest evidence for effectiveness but that it should only be used in exceptional circumstances when metoclopramide or erythromycin have not been effective, based on the recent safety issues highlighted by the MHRA. The type 2 diabetes guideline retains the recommendation to refer people with gastroparesis in circumstances where the differential diagnosis is in doubt or persistent or severe vomiting occurs.
492	Newcastle University	Full	290	l 26, rec 93:	The change in wording to 'large sudden' drop in visual acuity is not satisfactory, indeed dangerous wording. As VA is usually only	Thank for your comment. The advice of the diabetic eye screening programme was sought on these recommendations which have not been

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					measured yearly 'sudden' has no meaning. A confirmed drop of even one line can indicate development of macula oedema. Of course VA does fluctuate with a CV of one line in some people (partly with glucose control but also other eye problems and measurement conditions), so the key discriminator is confirmation (past measurements will be serial, current can be repeated), not 'large'. Large can be too late to be reversible. This rec is bad medical practice.	updated by an evidence review. The comment has been highlighted to the diabetic eye screening programme.
497	Newcastle University	Full	32 section 2.3	l 26-27	It might be worth pointing out that the guideline does not apply to common forms of diabetes often confused with type 2 diabetes, namely secondary diabetes (endocrinological or pancreatic).	Thank you for your feedback. The text has been amended.
495	Newcastle University	Full	32 section 2.2	l 4-6	This statement an oxymoron. Incidence is number of people per thousand developing diabetes per year, the figure of 1 in 20 is prevalence, and anyway merely an approximate restatement of the previous paragraph.	Thank you for your feedback. The text has been amended.
496	Newcastle University	Full	32 section 2.2	l 6-8	This sentence implies that the majority of people in certain ethnic groups have type 2 diabetes diagnosed before age 40 years. Simply wrong. In the next sentence 'age groups' are referred to without definition – 'at any age'. The general standard of English seems to have slipped from CG66/87 in 2008-9.	Thank you for your feedback. The text has been amended.
499	Newcastle University	Full	33 sectio	l 10-12	What is the relevance of this statement about children under 16 yr to a guideline specifically addressing those over 17 years?	Thank you for your comment. This is standard NICE template text which appears in all guidelines.

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			n 2.5,			
498	Newcastle University	Full	33 section 2.5	l 1-2	Is this true ('younger adults')? Perhaps the NICE rejected most of the evidence from the RCTs, but typical mean age for these is late 50's or more (see indeed Table 45). Even to some senior citizens this is middle-age – 'younger adults' would usually imply age 18-35 years. It is true that older RCTs did tend to have cut-offs of age 75 yr (now no longer true) so the 'elderly' were excluded, but this does not justify the misleading term 'younger adults'.	Thank you for your feedback. The text has been amended.
500	Newcastle University	Full	35 section 3.2.1	l 15-16	This is not true for people on insulin therapy as the guideline recognizes elsewhere, and indeed recommends. Did any diabetes health professional review this text? It appears there have been procedural failures here.	Thank you for your feedback. The text has been amended.
501	Newcastle University	Full	35 section 3.2.4	l 29-33	This is an extraordinary statement, and is fundamentally flawed. Firstly when considering individual medication (or class indications) specific adverse events are of course important. Examples would be lactic acidosis for metformin, and fractures, heart failure, fluid retention and bladder cancer for pioglitazone. More generally the evidence from questionnaire studies is that the comparative adverse outcomes which matter to people with diabetes are hypoglycaemia and weight gain – reported in most studies, and accounting for the separate approach in the next two sections. The GDG, searches, and HE analysis did not ignore these – see what follows.	Thank you for your feedback. As indicated in your comment, hypoglycaemia and weight gain are important outcomes for patients, which is why these outcomes were reported separately. Lines 29-33 refer to other adverse events and comparing these across different drugs/classes and studies.

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502	Newcastle University	Full	36 section 3.3.1 et seq:	l 29 et seq	It is not made clear this section and the next refers to surrogate outcomes and perhaps adverse events and not to true health outcomes. When considering true outcomes (notably vascular disease) a different time series would be used extending perhaps from 3 years to 30 years or more. Thus UKPDS and a few studies since.	Thank you for your feedback. While HbA1c is a surrogate outcome, other true health outcomes such as hypoglycaemia, weight gain and adverse events have been considered. It is necessary and well accepted that the best available method of predicting microvascular and macrovascular complications is by extrapolation from surrogate outcomes like HbA1c.
503	Newcastle University	Full Also appendix J	37 section 3.4.1:	l 32	My comment does not relate to data imputation but an issue related to change from baseline addressed in this section. It is well documented in glucose-lowering trials that the principal determinant of change in HbA1c is baseline HbA1c and not the therapy of study. I cannot see that correction has been made for this – without it the comparative analyses would usually be regarded as flawed. However I would accept that use of only differences from control studies (placebo or active) would partially mitigate the effect..	Thank you for your feedback. As outlined in section 3.6.2.9 of the guideline, use of baseline HbA1c as a covariate was explored. It was not used in the network meta-analyses to produce relative treatment effects, but was used in the health economic modelling to produce absolute treatment effects (appendix F 3.5.1)
504	Newcastle University	Full	38 3.4.2	l 14-15:	'When events are likely to occur to a person more than once (for example, hypoglycaemic events), it is preferable to use count or rate data.' This is not correct for hypoglycaemia in particular. Event rate and proportion affected can both be important numbers for clinical practice, although often both are not reported in oral agent (usually proportion) as opposed to insulin studies. The problem is that the distribution curve of hypoglycaemia is a decay curve, most events occurring in very few people.	Thank you for your feedback. The implications of hypoglycaemic events, with regard to both impact on the patient's quality of life and healthcare resource use and costs, will be critically dependent on the number of events each person experiences. The guideline development group (GDG) and developers considered it unacceptable to discard this information and focus, instead, on the probability that individuals would experience 1 or more event. The kind of significant event cited in the

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					Obviously if most events are occurring in <2 % of the population then rate (events/person-year) is a highly misleading statistic not applicable to 98% (and easily clinically managed by changing therapy). Here people/proportion affected (say the 30% of people have at least one event) is more clinically important – one fall in an old lady or collapse when shopping is the risk that matters. People/proportion affected also gives prediction of a much bigger health care burden, in practice is a more informative for oral agents, and more statistically powerful even for insulin in type 2 diabetes (because multiple events in one person are correctly not treated as independent by the usual C-M-H analysis) (not true of type 1 diabetes). I note that any meta-analysis or network analysis that does not take account of hypoglycaemia event distribution within each study is invalid (not true of number or people affected/proportion data). This comment applies to the usual definitions of hypoglycaemia (confirmed; documented symptomatic). For the hospitalizations it is perhaps not true, and for 'severe' (requiring third party assistance) it has less impact.	feedback is more likely to happen if patients experience multiple episodes, and this should not be ignored. From a health economic modelling perspective, even if probability of event was used as the input of interest, it would be necessary to estimate number of events separately, and this would be mathematically equivalent to – though less robustly parameterised than – relying on rate data. The point that experience of hypoglycaemia may be an impetus for switching therapy is a potentially important one. The HE model includes 2 causes of treatment discontinuation – inadequate control of HbA1c and withdrawal due to AEs. We assume that, in a good number of the cases reported in trials, the latter type of discontinuation reflects experience of hypoglycaemia. If so, this eventuality will be adequately reflected in the model. However, if it is the case that people in trials will tolerate a higher incidence of hypoglycaemia than would be seen in practice, the model will overestimate the amount of time people spend on treatments that are associated with higher incidence of hypoglycaemia and it will overestimate the costs and quality of life implications for those treatments.
476	Newcastle University	Appendix F	82	3.8	The newly introduced GLP-1 agents albiglutide and dulaglutide do not seem to be included, perhaps understandably, nor the change in exenatide MR device to the Bydureon Pen.	Thank you for your feedback. Included treatment options were limited to those for whom evidence was found.

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					Indeed it seems 'exenatide' is often terminologically used for exenatide IR in this section (incorrectly), and exenatide MR, on the market for some time ignored. In Table 6 In Table 42, page 169, the exenatide MR dose is tellingly missing.	Exenatide modified-release was not included in the health economic modelling as data were not available for all 4 outcomes.
473	Newcastle University	Appendix F	86	Table 65	There is a suspicion that the repaglinide unit mg drug cost here is wrong. Since I do not have access to the specific NHS Drug Tariff versions used I cannot be specific. However the drug is given tds ('with main meals', and supplied in blisters of 90) so the 4 mg or 3.96 mg assumed is a combination of use of 0.5 mg tds, 1 mg tds, and 2 mg tds. Both 0.5 mg and 1 mg are much more expensive per mg than 2 mg per mg dose, so the mix is critical to cost. 2x2 mg will severely underestimate acquisition cost. 1 mg tds will dominate proportionately, but the exact mix will have to be guessed. Perhaps 0.67 using 3x1 mg, 0.25 using 3x2 mg and the rest 3x0.5 mg?	Thank you for your feedback. The methods used to derive unit costs are detailed in appendix F section 3.8.3 and were agreed by the guideline development group. In line with your suggestion, it would have been possible to adopt an alternative approach that aimed to reflect currently prevailing – though not necessarily optimal – prescribing patterns. This would have had implications not only for the cost of repaglinide, but for all treatment options considered. However, the view of NICE and the guideline development group was that, on this occasion any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
474	Newcastle University	Appendix F	86	Table 65	Although not likely to have a large effect the assumptions of SMPG monitoring use with	Thank you for this comment, which calls for further analysis. It was considered alongside all

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					insulin and even injection number (needle use) appear wrong in this table. For example basal insulin with glargine is mainly titrated on 1 SMPG per day, somewhat higher for detemir (often used bd), and around double for NPH which is usually given twice daily and gives more hypoglycaemia. Conventional premixes require more than NPH for the same reason. On injection number IDegAsp will often be given (perhaps usually) twice a day, and was so in some of the studies evidenced.	other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
475	Newcastle University	Appendix F	86	Table 65	By around 4-5 years after starting insulin around 50% will be using a basal + meal-time multiple injection insulin regimen – this does not appear here at all. See CREDIT study in DRCP for evolution of regimens in developed nations.	Thank you for your feedback. No clinical evidence was included covering basal + meal time multiple injection regimes (see full guideline 8.4.16). Therefore such treatment options were not included in the health economic modelling.
470	Newcastle University	Appendix F	88	Table 65	There appears to be major error in SMPG assumptions. Sulfonylureas are assumed to require 3/week and repaglinide none. Both are insulin secretagogues working on the same cellular mechanism and both cause hypoglycaemia. Further the tds administration of repaglinide usually means more strips are used than for gliclazide (the main SU you assume). Since SMPG costs exceed drug acquisition costs this is likely to have significant effects on treatment costs and differences between these insulin secretagogues.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what

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					Indeed this more than accounts for the difference between SU and repaglinide in Table 66 (Annual treatment costs) – SU should be lower cost	stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
471	Newcastle University	Appendix F	88	Table 65	There appears to be major error in SMPG assumptions. Pioglitazone does not cause hypoglycaemia and used as monotherapy does not per se require SMPG. Your SMPG recommendations seem only to be for those at risk. This misjudgement extends to metformin-pioglitazone (again does not cause hypoglycaemia), and the GLP-1RA agents in combination with metformin, none of which carries a hypoglycaemia risk in this situation.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
472	Newcastle University	Appendix F	88	Table 65	The assumed rates of SMPG use with sulfonylureas (and indeed with repaglinide) differ according to use in combination or otherwise. Essentially combination of any agent with an insulin secretagogue enhances the rate of hypoglycaemia (many many studies). A reasonable assumption might be that your SMPG rate of 3/week is correct for combination therapy where one agent or more is a sulfonylurea, but for monotherapy rates (except in cases of occupational risk – low proportion)	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and

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					would be better modelled at 1/week. For repaglinide see below, comment 8, sub-point 4, which deals with the higher rate of SMPG use with this drug.	health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
505	Newcastle University	Full	98	l 28 8.1.1 .2	This is a very odd statement about rosiglitazone. As a result of the RECORD study re-examination by the FDA the drug has been returned without restriction to the US market, and the US label (SmPC equivalent) only warns about heart failure, as class effect. In Europe it remains suspended, but because the manufacturer has not been motivated to ask for review of the issues. It is possible the GDG opinion, always naive, predated the FDA/Duke reviews. The rosi papers have useful comparative information (eg sulfonylurea vs metformin) anyway, and similarly network information independent of rosiglitazone, so it anyway appears to have been illogical and perverse to exclude them. There is some very strong data here.	Thank you for your feedback. Rosiglitazone comparisons were excluded. However, where studies included multiple arms with comparisons of interest for example, metformin versus placebo, such data were extracted.
481	Newcastle University	Full	General	General	Unlike the SGLT2i's (previous point) the guideline also has the problem that several other newly marketed products are appearing/have appeared in 2015. Thus the new formulation of exenatide MR (pen), albiglutide, dulaglutide, biosimilar insulin glargine (Lilly), other SGLT2's. This commentator would accept these probably cannot make the current version of the	Thank you for your comment. NICE cannot provide comment on biosimilars within the guidance until such time they become available. Please see the NICE position statement on biosimilars. However, the suggestion has been logged so it can be taken account of when the guideline is considered for update.

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					guideline, but it does suggest a rapid update will be required within 12 months. Indeed given the pace of change in glucose-lowering medications should this not be a living guideline with yearly updates?	
238	NHS Choices	NICE	General	General	We welcome the guidance. After consultation we have no comments.	Thank you for your feedback.
336	NHS England	NICE	General	General	Given that over 5% of the population of England (and over 6% in Wales) have Type 2 diabetes, the reach of this particular guidance is great, and it's potential for tackling morbidity, mortality and NHS costs related to the health of this large proportion of the population is significant. It is cause for concern therefore that the drug treatments suggested do not well reflect current practice, and some reflect practice that we left behind, what many will feel for very good reasons, some time ago. On the whole, the guidance around drug treatment is difficult to follow, and lacks the clarity of preceding NICE Guidance for Type 2 diabetes. The specific drugs recommended seem to arise from network meta-analysis. The vast majority of diabetes health care professionals, including consultant diabetologists, will not know what this is, and the fact that the network meta-analysis has produced treatment suggestions that are counter-intuitive and very different to current clinical practice, undermines the credibility of the	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

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					output and of the guidance itself.	
337	NHS England	NICE	General	General	Repaglinide (1.6.19) – most clinicians in the UK caring for people with Type 2 diabetes have no experience in use of this drug, despite it having been available now for many years. There is also little suggestion of using repaglinide in international guidelines - in the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines the meglitinides are virtually not mentioned at all. A systematic review and mixed-treatment comparison meta-analysis by McIntosh et al. (Open Medicine 2011;5(1):E35-E48) looked at classes of drugs added second line to Metformin, and showed that meglitinides including repaglinide have no other advantage compared to sulfonylureas in either weight gain or hypoglycaemia risk when added to Metformin. Perhaps an isolated situation where repaglinide may seem an intuitive treatment is when fasting during the period of Ramadan. There have been a few studies that have shown some small advantage of repaglinide when used in this setting (Mafauzy M. Repaglinide versus glibenclamide treatment of type 2 diabetes during Ramadan fasting. Diabetes Res Clin Pract 2002;58(1):45-53); however, other studies show no advantage of repaglinide over sulphonylureas in this situation (Anwar A, Azmi KN, Hamidon BB, Khalid BA. An open label	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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					comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. Medical Journal of Malaysia 2006;61:28-35). The thrice daily dose scheduling of repaglinide will result in much lower concordance. Also, escalation from repaglinide monotherapy requires discontinuation followed by stepwise introduction of two agents, necessitating greater number of consultations in a capacity limited system. Presumably the additional resulting consultations were not entered into the cost effectiveness analysis.	
338	NHS England	NICE	General	General	Pioglitazone (1.6.20) – after the withdrawal of the two preceding drugs in this class (troglitazone and rosiglitazone) for safety reasons, and indeed taking into account the safety concerns around pioglitazone itself with regard heart failure, fractures, and bladder cancer (resulting in withdrawal in France and Germany), many clinicians stopped writing new prescriptions for pioglitazone around 2 years ago. The prominent recommendation for pioglitazone in this guideline therefore goes against current clinical practice, formed out of genuine clinical concerns around safety.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At initial therapy, the guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin:

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						pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been also added to the recommendations and algorithm.
339	NHS England	NICE	General	General	Given the role in weight gain / obesity in driving the increasing prevalence of Type 2 diabetes, the roles of other weight-neutral or indeed weight loss-promoting therapies appear to be understated (GLP-1 agonists, DPP4-inhibitors, SGL2-inhibitors), despite previous positive NICE Technology Assessments of such agents. The SGL2-inhibitors get very little mention in the consultation guideline.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis, and not only the available licensed combinations. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At initial therapy, the guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the

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						normal process for assessing the need to update TA guidance.
340	NHS England	NICE	General	General	There is no information as to whether slow-release metformin preparations were considered at all. Many clinicians consider their use when people are intolerant of standard release metformin monotherapy.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
341	NHS England	NICE	General	General	The recently published obesity guideline, NICE CG189, expanded the inclusion criteria for consideration of bariatric surgery for those with Type 2 diabetes, yet there is no mention in the current consultation Type 2 diabetes guideline as to where bariatric surgery may sit in the clinical pathway. This needs to be cross referenced.	Thank you for your feedback. A cross reference to CG189 has now been added to the end of the section on Dietary Advice within the guideline.
342	NHS England	NICE	General	General	Once daily NPH insulin is suggested at bed time (1.6.34). Why not in the morning? The duration of action is less than 24 hours, and greatest glycaemic excursions will be in the day time. Morning administration would also mitigate against the risk of night time hypoglycaemia.	Thank you for your feedback. This part of recommendation 1.6.33 (NICE version) has been changed to "*Offer NPH insulin injected once or twice daily according to need.*"
343	NHS England	NICE	General	General	1.4.8 - For Africans and Caribbeans, the guideline suggests starting two anti hypertensive agents simultaneously as first line treatment of hypertension. In this situation, stepwise	Thank you for your feedback. Blood pressure therapy was not prioritised for update within this iteration of the type 2 diabetes guideline following the stakeholder workshop and

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					introduction of two agents would be more usual clinical practice.	stakeholder consultation during the scoping phase. As no new evidence review has been conducted, it is not possible to make changes to these recommendations. However, the suggestion has been logged and will be taken into account when the guideline is next considered for update**.**
77	NHS Nene CCG	Full	15		In the algorithm on page 15 (second intensification) the question "HbA1c< 58mmol/mol (7.5%)?" with regards to whether to switch from NPH insulin to an analogue insulin, is not qualified with the text, "because of significant hypoglycaemia" which appears on page 23, line 35 & 36 (and page 258, lines 26 & 27). It is important to include this text as this will be misinterpreted if it is omitted from the algorithm. It is likely to be the algorithm which is used in clinical practice, without reference to the text.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and reflect the amended recommendations that place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
82	NHS Nene CCG	Full	18 (and 81)	15 (P81 line 37)	Suggest that the wording is amended to "substitute a generic angiotensin II receptor antagonist for the ACE inhibitor".	Thank you for your feedback. The section on blood pressure therapy within the type 2 diabetes guideline was not prioritised for update following the stakeholder workshop and stakeholder consultation during the scoping phase. As no new evidence review has been conducted, it is not possible to change recommendations in this area of the guideline.
81	NHS Nene CCG	Full	18 (and	18 (P82, line	It states, "usually a thiazide or thiazide-like diuretic". Should this be changed to match the Hypertension CG 127 which states, "If diuretic	Thank you for your feedback. NICE clinical guideline 127, Hypertension (2011) did not specifically include people with diabetes in the

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			82)	41)	treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide"? If this is not made consistent then patients with type 2 diabetes and hypertension could be initiated on bendroflumethiazide, whereas other patients would not be.	evidence base. Therefore the hypertension guidance cross refers to recommendations on blood pressure management in people with type 2 diabetes, in the Type 2 diabetes guideline. This section of the type 2 diabetes guideline was not prioritised for update following the stakeholder workshop and stakeholder consultation during the scoping phase. The recommendations have been brought forward from the previous iteration of the guideline. As no new evidence review have been conducted, it is not possible to make any changes to these recommendations.
80	NHS Nene CCG	Full	197 , 198		On page 197 it is acknowledged that "The GDG agreed that, while standard-release metformin was not associated with the greatest reduction in HbA1c in the reviewed evidence, the additional cardiovascular benefits associated with metformin use are very important in the overall long-term management of the individual with type 2 diabetes". It appears that the CV benefits of metformin were not considered formally elsewhere in the clinical and economic assessments, so has this been fully considered in terms of the potential benefit of modified-release metformin? On page 198 it states, "The GDG noted that there was limited evidence on alternative forms of metformin for individuals who cannot tolerate standard-release metformin". Accepting that the evidence for improved	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.

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					tolerability over the standard-release formulation is limited, it would still have seemed pragmatic to include m/r metformin as an option if s/r metformin is not tolerated, ahead of repaglinide, as the benefits of being on metformin *per se* are significant from a CV perspective. UKPDS 34. Lancet 1998; 352:854–865	
83	NHS Nene CCG	Full	22 (and 257)	40 (P257, line 21)	Would support the statement to, "Only offer a GLP-1 mimetic in combination with insulin in a specialist care setting" due to the lack of evidence to support this combination. However, it would be useful to include some criteria that would be expected to be achieved in order for this combination to be considered cost-effective and hence continued (as there is for GLP-1 mimetics alone). Without criteria co-prescribing of GLP-1 mimetics and insulin could be continued indefinitely.	Thank you for your feedback and suggestion. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
78	NHS Nene CCG	Full	23	35,36	Text needs to be included fully in the algorithm, as above	Thank you for your feedback. The circumstances to switch from NPH insulin to insulin detemir or glargine have been included in the algorithm.
79	NHS Nene CCG	Full	258	26,27	Text needs to be included fully in the algorithm, as above	Thank you for your feedback. The circumstances to switch from NPH insulin to insulin detemir or glargine have been included in the algorithm.
524	North & East London Commissioning Support Unit	Full	166	24 -25	Where is the evidence for this statement?	Thank you for your feedback. The principle for intensification and selecting drugs that are complementary is based on the guideline development group's clinical expertise.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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525	North & East London Commissioning Support Unit	Full	167	18 -34	Classifying treatments in this manner subsequently created a complex mix of therapies, made even more complicated in the proposed implementation through constraints of licence, drug interactions with medication for co-morbidities and adverse effects in patients with co-morbidity (e.g. heart failure) The caveats advised at the beginning (e.g. may not be applicable to elderly etc) make implementation even more complex. This results in a simple treatment intensification algorithm changing into a very complex series of drug treatment choices, the last of which has no recommendation. On the ground, faced with people with mullti-morbidity, there may be too much for patients and healthcare professionals to discuss and agree on, and poor decision making may result in harm This complexity may detract from the guideline as a whole, rendering implementation difficult.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
523	North & East London Commissioning Support Unit	Full	General	General	Overall comment: This is a very good guideline for the most part, providing useful help and guidance for the care of people with Type II Diabetes to improve service delivery. However, the latter part on management of blood glucose appears complex and difficult to understand and therefore implement	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice

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						around which pharmacological interventions are appropriate for consideration.
389	North Central London Joint Formulary Committee	Full	12	1	is 53mmol/mol(7.0%) reasonable as a general target for intensification? Important that if 53mmol/mol is the target that is not a stringent target for everyone.	Thank you for your feedback. The recommendation provides a drug intensification threshold of 58 mmol/mol (7.5%) with an associated target set at 53 mmol/mol (7%). A drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) was not selected as it was considered too low and inappropriate for most people as the condition progresses. The guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and therefore has included recommendations 1.6.5 and 1.6.9 (in the NICE version) with associated commentary documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
390	North Central London Joint Formulary Committee	Full	12	1	patients should be involved in target and goal setting and that potential harms of too low an HbA1c target are discussed with patient.	Thank you for your feedback. Patients should be involved in target setting and a comprehensive discussion of potential harms should be included in the consultation (please see recommendation 1.6.5 in the NICE version).
391	North Central London Joint Formulary	Full	12	1	Previous guideline suggested agreeing stepwise targets with patients-this guideline appears to move away from this.	Thank you for your feedback. The "stepwise targets" recommendation in CG66 states: *"When setting a target glycated haemoglobin HbA1c:*

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	Committee					● *involve the person in decisions about their individual HbA1c target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general* ● *encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life* ● *offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level* ● *inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health* ● *avoid pursuing highly intensive management to levels of less than 6.5 %."* These elements have been incorporated in the different recommendations on targets (see recommendations 1.6.5 to 1.6.10 in the NICE version).
392	North Central London Joint Formulary Committee	Full	12	1	Good that major emphasis of guidelines is to educate patients and involve them in goal setting.	Thank you for your feedback.
393	North Central London Joint	Full	12	1	Would a more appropriate target be to intensify to 58mmol/mol(7.5%) for most patients as lowering HbA1c for most patients is likely to lead to more side effects with little effect on	Thank you for your feedback. The recommendation provides a drug intensification threshold of 58 mmol/mol (7.5%) with an associated target set at 53 mmol/mol (7%). A

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	Formulary Committee				outcomes?	drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) was not selected as it was considered too low and inappropriate for most people as the condition progresses. The guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and therefore has included recommendations 1.6.5 and 1.6.9 (in the NICE version) with associated commentary documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
394	North Central London Joint Formulary Committee	Full	12	19	why is repaglinide included at this stage and what is the evidence base for repaglinide rather than an alternative eg sulphonylurea?	Thank you for your feedback. The guideline development group (GDG) considered repaglinide, which was shown to be consistently associated with the largest reduction in HbA1c at 3, 6 and 12 months, but also with a greater number of hypoglycaemic events. The GDG noted that the occurrence of hypoglycaemic events was consistent with their experience in clinical practice. The GDG considered the change in body weight associated with repaglinide, and agreed that while it was associated with weight gain it fared better than sulfonylureas for this outcome. The GDG recognised that repaglinide is a secretagogue not widely used in current UK clinical practice and that a recommendation to offer repaglinide as an alternative initial therapy when metformin is contraindicated or not tolerated would lead to a

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						large change in practice but considered that the consistent findings of significantly large clinically important reductions in HbA1c up to 1 year shown in the evidence justified the recommendation. The GDG group noted that, although sulfonylureas were associated with clinically important reductions in HbA1c in the short term at 3 and 6 months, they were consistently associated with greater hypoglycaemic events and weight gain at 12 and 24 months. The GDG noted that the occurrence of hypoglycaemic events was consistent with their experiences in clinical practice. The GDG discussed the value of using sulfonylureas to achieve rapid blood glucose control (rescue therapy) in clinical practice, but considered that the use of sulfonylureas as an immediate second option if metformin is contraindicated or not tolerated was not supported by the evidence base, because of the short-term efficacy in change in HbA1c and associated increased risks of adverse events including hypoglycaemia. The GDG agreed that use of sulfonylurea as rescue therapy should consider the balance of good glycaemic control and the risk of poor weight outcomes and hypoglycaemia in discussion with patients and therefore, treatment should be reviewed once agreed targets have been met.
39	North	Full	12	19	Decision to include repaglinide in this position	Thank you for your feedback. The guideline

Type 2 diabetes (update)

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Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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5	Central London Joint Formulary Committee				needs explaining in more detail. Need evidence behind decisions and its superiority to sulphonylureas. Has the increased tablet burden and adherence issues with taking a med TDS pre meals compared with OD or BD dosing been taken into account.	development group (GDG) considered repaglinide, which was shown to be consistently associated with the largest reduction in HbA1c at 3, 6 and 12 months, but also with a greater number of hypoglycaemic events. The GDG noted that the occurrence of hypoglycaemic events was consistent with their experience in clinical practice. The GDG considered the change in body weight associated with repaglinide, and agreed that while it was associated with weight gain it fared better than sulfonylureas for this outcome. The GDG recognised that repaglinide is a secretagogue not widely used in current UK clinical practice and that a recommendation to offer repaglinide as an alternative initial therapy when metformin is contraindicated or not tolerated would lead to a large change in practice but considered that the consistent findings of significantly large clinically important reductions in HbA1c up to 1 year shown in the evidence justified the recommendation. The GDG group noted that, although sulfonylureas were associated with clinically important reductions in HbA1c in the short term at 3 and 6 months, they were consistently associated with greater hypoglycaemic events and weight gain at 12 and 24 months. The GDG noted that the occurrence of hypoglycaemic events was consistent with their experiences in

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						clinical practice. The GDG discussed the value of using sulfonylureas to achieve rapid blood glucose control (rescue therapy) in clinical practice, but considered that the use of sulfonylureas as an immediate second option if metformin is contraindicated or not tolerated was not supported by the evidence base, because of the short-term efficacy in change in HbA1c and associated increased risks of adverse events including hypoglycaemia. The GDG agreed that use of sulfonylurea as rescue therapy should consider the balance of good glycaemic control and the risk of poor weight outcomes and hypoglycaemia in discussion with patients and therefore, treatment should be reviewed once agreed targets have been met.
396	North Central London Joint Formulary Committee	Full	12	21	what is the risk of bladder cancer using pioglitazone? and can a tool (patient decision aid) be provided which can be used to calculate the risk and explain it to patients.	Thank you for your comment. The MHRA states that a European review "…found a small increased risk of bladder cancer in patients taking pioglitazone; however, the benefits continue to outweigh the risks for those who respond to treatment and in whom there are no identified risk factors for bladder cancer. Observational studies report relative risks ranging from 1.12 to 1.33 when diabetic patients receiving pioglitazone are compared with diabetic patients receiving other antidiabetic medicines but not exposed to pioglitazone. The increase in absolute risk is therefore likely to be small. Whether the increased risk occurs early in treatment or only after prolonged exposure

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						remains unclear." The suggestion of a patient decision aid will be passed on to the NICE guidance implementation team.
397	North Central London Joint Formulary Committee	Full	12	21	The contra-indications for Pioglitazone should be made clearer (e.g. heart failure and bladder Ca)	Thank you for your feedback. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
398	North Central London Joint Formulary Committee	Full	14	First Intensification algorithm	Figure 2 First Intensification algorithm- the flowchart states that at 1st intensification regimens SGLT2s may be appropriate for some people but are beyond the scope of this guideline.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
399	North Central London Joint Formulary Committee	Full	14	First Intensification algorithm	NICE have issued TAGs on SGLT2s(Dapagliflozin and Canagliflozin and consequently it seems ridiculous that there is no reference ,apart from 1st intensification algorithm, to the use of these drugs in this guidelines. Some statement about place of SGLT2 should be included eg should not be used until 2nd intensification.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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						TA guidance. A reference box to NICE TAs for SGLT-2 inhibitors is included in the algorithms for first and second intensification.
400	North Central London Joint Formulary Committee	Full	14	First Intensification algorithm	Metformin Contra indicated or not tolerated seems to follow different pathway from 1st intensification-why?	Thank you for your feedback. The rationale for the recommended options is found in Section 8.4.11 of the full guideline.
401	North Central London Joint Formulary Committee	Full	16	9	Good that reference is made to stopping ineffective medicines.	Thank you for your feedback.
402	North Central London Joint Formulary Committee	Full	19	35	Good that it recommends relaxing target HbA1c but patients examples of targets should be included as guidance to prescribers in setting targets eg IDF suggest 69mmol/mol(8.5%) for patients with dementia.	Thank you for your feedback and agreement with the recommendation to consider relaxing blood glucose targets in different circumstances. For clarity, the guideline development group considered that it would not be useful to provide specific guidance on individual clinical scenarios.
403	North Central London Joint Formulary Committe	Full	22	8	starting insulin-based treatment-guideline does not seem to rank insulin therapy very highly-could advice be given to suggest which patients are likely to benefit most from insulin therapy eg those with HbA1c>75mmol/mol(9.0%).	Thank you for your feedback. The guideline recommends starting insulin-based treatment as rescue therapy at any point in the pathway for people who are symptomatically hyperglycaemic (recommendation 1.6.18) and when blood glucose levels are inadequately controlled by

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	e					dual oral therapy.
404	North Central London Joint Formulary Committee	Full	22	8	Insulin place in therapy could be made clearer/bolder.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
405	North Central London Joint Formulary Committee	Full	23	13	there should be more emphasis on use of NPH insulin rather than analogues.	Thank you for your feedback. NPH insulin is recommended as the first option in recommendation 1.6.33 (NICE version).
406	North Central London Joint Formulary Committee	Full	23	13	Could NICE also include an anticipatory comment about biosimilar insulins and their place in therapy (e.g. switching current patients or only using biosimilars on new patients)?	Thank you for your comment. NICE cannot provide comment on biosimilars within the guidance until such time they become available. Please see the NICE position statement on biosimilars.
802	North of England Commissioning	Full	13 ,14,1		**Algorithm** • Need to add rescue treatment with insulin in the algorithm across the sides • Presentation difficult to follow (although	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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	Support		5		breaking up into first, second- intensification, etc. is helpful) – more use of colour to delineate different "strands" might help.	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page, including rescue treatment with insulin or sulfonylurea illustrated.
798	North of England Commissioning Support	NICE	22	1.6.19 and 1.6.20	**Initial treatment - repaglinide** **Our concerns are:** • repaglinide is not currently in common use. • combination treatment – repaglinide is only licensed for use with metformin, hence at first intensification of treatment, two new drugs will need to be added **Initial treatment – pioglitazone** We do not agree with pioglitazone as first option at this point because of fracture risk Our suggestions are: • Add metformin SR for those with abdominal side effects • Because of fracture risk and heart failure with pioglitazone, make DPP-4 inhibitor the option here.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
799	North of England Commissioning Support	NICE	22	1.6.22	**First intensification** As above re pioglitazone and adverse effects – we would welcome the analysis being re-evaluated with "more explicit consideration of impact of risks of fracture on cost-effectiveness".	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of

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						limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
800	North of England Commissioning Support	NICE	27	1.6.34	**Non-analogue insulin use** We question: • the positioning of analogues as alternatives to NPH when control not adequate due to significant hypos – as not straightforwardly evidence based (no difference in overall or severe hypos, only nocturnal, and (perhaps more importantly) not clearly set out in algorithm where is abbreviated to give impression that analogues are recommended when HbA1c not achieved for ANY reason with NPH. • "Consider pre-mixed preparations that include short-acting insulin analogues*, rather than pre-mixed preparations that include short-acting human insulin preparations, if:* - *a person prefers injecting insulin immediately before a meal, or* - *hypoglycaemia is a problem, or* - *blood glucose levels rise markedly after meals"*	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

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					Comparative Effectiveness Review - Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes http://www.effectivehealthcare.ahrq.gov/ehc/products/18/106/2008_0915InsulinAnaloguesFinal.pdf Found 16 studies that compared premixed insulin analogues with premixed human insulin. Premixed insulin analogues and premixed human insulin appeared to be similarly effective in lowering fasting glucose. Premixed insulin analogues were more effective in lowering postprandial glucose (by around 1mmol/L – is this short effect clinically significant). Premixed insulin analogues appeared to be similar to premixed human insulin in lowering A1c levels and the incidence of hypoglycemia.	
801	North of England Commissioning Support	NICE	General		**GLP1** The use of GLP1 may need to be reviewed, once we have reliable evidence regarding effects on complications with longer-term use. Until then, stick with recommendations based on original cost-effectiveness analysis.	Thank you for your feedback.
803	North of England Commissioning Support	Full	General		**Missing from guideline** Biosimilar analogues and SGLT-2 drugs	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the

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						changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. NICE cannot provide comment on biosimilars within the guidance until such time they become available. Please see the NICE position statement on biosimilars.
720	North West Commissioning Support Unit	NICE (and respectively full version)	8		On what basis are the changes affecting treatment of erectile dysfunction classed as new? There is a new legislation removing the SLS restriction on prescribing of sildenafil; however, this is not reflected in draft document. Existing guideline already suggests using PDE5 inhibitor with lowest cost.	Thank you for your feedback. At this update, the clinical and cost effectiveness evidence for PDE-5 inhibitors was reviewed. Based on the evidence, the recommendation from CG66 was weakened from an "***Offer*** *a phosphodiesterase-5 inhibitor (choosing the drug with the lowest acquisition cost), in the absence of contraindications, if erectile dysfunction is a problem*" to a "***Consider*** *a phosphodiesterase-5 inhibitor to treat problematic erectile dysfunction, initially choosing the drug with the lowest acquisition cost and taking into account any contraindications*".
721	North West Commissioning Support Unit	NICE (and respectively full version)	8	top paragraph	Was it taken on account that by replacing the NICE TA203 and TA248 by a clinical guideline, the strength of recommendation changes and those treatments will no longer have to be made available to patients? Will the prescribing of liraglutide and exenatide for patients under existing TAs be scrutinised once TAs become obsolete?	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 (liraglutide) and NICE technology appraisal guidance 248 (exenatide prolonged-release). Based on the updated evidence review and health economic analysis, the guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care

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						setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
668	Novartis	Full	179 181 182	Figure 8 Figure 10 Figure 12 Figur	The importance of baseline HbA1c in the magnitude of the change in HbA1c is well established.[1] The methodology utilised by NICE did not adjust for the baseline HbA1c levels, and there was considerable variation in the average baseline HbA1c levels among the various drugs evaluated. We believe that this baseline	Thank you for your feedback. As outlined in section 3.6.2.9 of the guideline, use of baseline HbA1c as a covariate was explored. It was not used in the network meta-analyses to produce relative treatment effects, but was used in the health economic modelling to produce absolute treatment effects (appendix F 3.5.1).

[1]

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			183	e 14	variation in HbA1c has biased the relative effectiveness of the drugs evaluated. We therefore request that NICE rerun the analysis with an appropriate adjustment for baseline HbA1c. If this is not practical, then we request that where relative effectiveness is shown in figures 8, 10, 12 and 14, that this highlighted limitation be clearly and prominently displayed. (1) *Ahren et al Efficacy of vildagliptin versus sulfonylureas as add-on therapy to metformin: comparison of results from randomised controlled and observational studies. Diabetologia 2014 57:1304-1307*	
669	Novartis	Full	General (model)	General (model)	**Economic model review - Sheet "Model Settings"** Cell E6: Number of strategies - The default number is 7 and increasing strategies beyond 20 leads to the same strategies from 21 and beyond.	Thank you for your feedback. Data were only available for 20 strategies in the NICE model – should the user enter data for more than 20 strategies, the model would reflect these extra strategies.
670	Novartis	Full	General (model)	General (model)	**Economic model review – Sheet "model parameters"** Since the model is already compiling and adding the results outside of UKPDS, it would be appropriate to update the cost values since these values are from the year 2000. An example is "Cost of non-fatal IHD" which is considered as £3486.66. Recent studies[2] have reported the costs to be £9767 (£7038-£12 696). This is in contrast to MI costs which are nearly	Thank you for your feedback. Alternative cost sources were considered (see appendix F 3.8.1); updated UKPDS costs (as referenced) were not available at the time of modelling.

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					same. The implication on the model results is that drugs with varying efficacy on these two events are likely to show varying levels of cost-effectiveness in the real world which will be in contrary to the results predicted by the model. (2) *Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabet Med. 2014 Nov 29. doi: 10.1111/dme.12647. [Epub ahead ofprint] PubMed PMID: 25439048.*	
671	Novartis	Full	General (model)	General (model)l	**Economic model review – Sheet "Parameters":** Some of the costs used in the model do not match the costs from BNF 2014. E.g. Metformin: Cell G157. Pioglitazone: Cell G167	Thank you for your feedback. As per the NICE Guidelines Manual (2012), drug unit costs were taken from the NHS Drugs Tariff (July 2014 edition) and not the BNF.
672	Novartis	Full	General (model)	General (model)	**Economic model review – Sheet "Parameters":** Cell paramQALE1Blind – Disutility attributed to blindness (-0.074) seems to be low since this disutility is lower compared to disutility due to IHD, stroke etc. whereas intuitively this would be expected to be higher. It is possible that the disutility is for blindness in one eye and, if so, this needs to be explicitly mentioned.	Thank you for your feedback. The selection of utility values is fully defined and discussed in appendix F (3.10).
673	Novartis	Full	General	General	**Economic model review – Sheet "Parameters":**	Thank you for your feedback. Whilst this is a formatting error, it does not affect the working of the model and alternative values could be

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			(model)	(model)	The user input cells in section 'Hypoglycemia rates' (Cells E21:E30) have restricted inputs for the user. The data validations in these cells allow users to input only 1 and 2 as the values besides the base case default values.	specified by the user in column G.
674	Novartis	Full	General (model) & Table 46 page 178	General (model)	While there were no major comments on the sources used in the model, a better documentation of the network meta-analysis (NMA) would have ensured a better review. For example, including a measure of heterogeneity for the NMA and exploration of possible impacts of certain papers through a sensitivity analysis. The main drivers for the efficacy in the model are from a NMA undertaken by NICE. Since as we have already highlighted there is a variance in the baseline HBA1c, the heterogeneity of the studies is expected to be higher. The NICE document however fails to mention how the issue of heterogeneity was addressed and if any further sensitivity analysis was performed. However, the potential for bias was recognised within the document as illustrated in table 46 (change in blood glucose (HbA1c)). Within this table risk of bias was rated "serious", 12 months imprecision was also rated "serious" and quality was rated "low". The results generated from the model will only be as good as the efficacy inputs included within it, i.e. the NMA performed by NICE. With the potential for increased bias, the resulting ICERs values are likely to be subject to	Thank you for your feedback. As outlined in section 3.6.2.9 of the guideline, use of baseline HbA1c as a covariate was explored. It was not used in the network meta-analyses (NMAs) to produce relative treatment effects, but was used in the health economic modelling to produce absolute treatment effects (appendix F 3.5.1). As outlined in section 3.6.2.10 of the guideline, the use of inconsistency models to explore potential heterogeneity was undertaken.

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					considerably uncertainty resulting from the issues we have highlighted.	
744	Novo Nordisk Ltd	NICE	11	Targets	*"Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia"* It should be noted that if hypoglycaemia is restricting the attainment of glycaemic targets, the recommendation should be to consider switching to a regimen with a lower risk of hypoglycaemia. The GAPP2 study (doi:10.1016/j.pcd.2012.10.059) has shown that hypoglycaemia is a limiting factor preventing patients from achieving optimal blood glucose control.	Thank you for your feedback. This is a generic recommendation on patient care in agreeing, setting and monitoring individual HbA1c targets. Hypoglycaemia was provided as an example of a possible adverse effect of treatment. It is beyond the remit of this recommendation to prescribe management for the specific adverse effect of hypoglycaemia.
797	Novo Nordisk Ltd	Appendix F	114		It is apparent from table 82 that there has been no cost applied for events of hypoglycaemia that were not severe – despite evidence to the contrary. Events of non-severe hypoglycaemia will as a minimum result in additional blood glucose monitoring, as well as resulting in contact with a GP or specialist in a proportion of cases (Brod 2009, doi:10.1016/j.jval.2011.02.001). In addition to the costs outside the NHS that are borne by the patients. These costs should be included in the cost-effectiveness analysis.	Thank you for your feedback. As stated in appendix F 3.9.4, non-severe hypoglycaemic episodes were defined by the guideline development group as those episodes where people were able to treat themselves and were therefore assumed to not incur any NHS resource use or cost.
749	Novo Nordisk Ltd	Full	15	Sec 1.4	**Figure 3: Pharmacological treatment algorithm – second intensification** Despite the recognition of the place in therapy	Thank you for your feedback. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.

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					for GLP-1 analogues in the full guideline, these have been omitted from the treatment algorithm. We can only assume that this is an error caused by the graphics team having to generate a complex algorithm. And await their inclusion in the final version.	
750	Novo Nordisk Ltd	Full	15	Sec 1.4	**Figure 3: Pharmacological treatment algorithm – second intensification** We suggest that in the insulin section of the algorithm, the option of a basal-bolus insulin regimen is made explicitly clear. Since this has advantages in certain patients.	Thank you for your feedback. Recommendations 1.6.35 and 1.6.36 (NICE version) provide situations where basal-bolus insulin regimens should be considered: 1.6.35 *Monitor people with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation).* 1.6.36 *Monitor people with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate.* The need to monitor is also reflected in the algorithm.
751	Novo Nordisk Ltd	Full	15	Sec 1.4	The treatment algorithm recommends isophane insulin initially, with a switch to basal analogues only after suffering hypoglycaemia on isophane. Novo Nordisk feels this is not in the patient's best interest. It would seem that NICE accepts that the longer-acting analogue insulins cause less hypoglycaemia as they recommend their	Thank you for your feedback. The recommendations in this guideline are based on the evaluated clinical effectiveness evidence review and health economic analyses specifically in people with type 2 diabetes which found NPH insulin to be the most cost-effective insulin-based option. It is inappropriate to extrapolate the

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					use first line in type 1 diabetes for this reason. Novo Nordisk believe that analogue insulins should also be positioned first line in the Type 2 guidelines.	recommendations from the Type 1 diabetes guideline.
762	Novo Nordisk Ltd	Full	15	Sec 1.4	**Figure 3: Pharmacological treatment algorithm – second intensification** Novo Nordisk endorses the approach to add insulin detemir if NPH is not appropriate. Insulin detemir allows for twice daily dosing in its license, unlike insulin glargine. This allows for flexibility in the regimen which can be of great value to certain patients. Also the overall data with insulin detemir demonstrates less weight gain in comparison to NPH and insulin glargine (Levemir® SPC). This would then also be more consistent with the Type 1 diabetes guideline	Thank you for your feedback.
763	Novo Nordisk Ltd	Full	15	Sec 1.4	**Figure 2: Pharmacological treatment algorithm – first intensification** Novo Nordisk suggest that it is made clear in the algorithm that there is the option of adding insulin earlier in the treatment pathway, for example in combination with metformin, for appropriate patients rather than going through a series of oral drugs first. There should also be an emphasis on avoiding clinical inertia in terms of moving onto other therapies if glucose targets are not being met within certain timelines.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

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764	Novo Nordisk Ltd	Full	15	Sec 1.4	**Figure 3: Pharmacological treatment algorithm – second intensification** There is an omission of insulin degludec from the treatment algorithm. This insulin has a clear place in therapy for certain patient populations and Novo Nordisk feel this should be clear on the treatment algorithm as an option. Insulin degludec is a basal insulin with a half-life of more than 25 hours, 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. More importantly, it may allow patients to improve glycaemic control with less risk of hypoglycaemia, particularly nocturnal confirmed hypoglycaemia when compared with insulin glargine. • A meta-analysis in type 2 diabetes confirmed significantly lower rates of confirmed hypoglycaemic events with insulin degludec than insulin glargine in the type 2 diabetes population. Insulin degludec also had significantly lower rates of nocturnal confirmed hypoglycaemic events than	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec–metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec–metformin, and subsequently it does not appear in the algorithm.

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					insulin glargine in the type 2 diabetes population (Ratner et al.*Diabetes Obes Metab* 2013 ;15: 175–184). • The rate of severe hypoglycaemia in type 2 basal-only therapy, was significantly lower for insulin degludec than for insulin glargine (Zinman et al. *Diabetes Care* 2012; 35:2464–2471. • A study by Hollander et al 2014 compared the long-term safety and efficacy of insulin degludec with insulin glargine in patients with advanced type 2 diabetes over 78 weeks. The study showed that patients with advanced type 2 diabetes who continued insulin degludec therapy experienced long-term improvements in glycaemic control similar to those treated with insulin glargine at similar doses, but with significantly lower risks of overall and nocturnal confirmed hypoglycaemia. (Hollander et al 2014 *Diabetes, Obesity and Metabolism.* doi:10.1111/dom.12411 5) • Elderly patients are generally more susceptible to hypoglycaemia due to longstanding disease, higher incidence of co-morbidities, reduced hypoglycaemic awareness and are more vulnerable if living alone. Therefore, the overall hypoglycaemia	

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					meta-analyses for degludec were repeated in elderly patients ≥65 years of age with either type 1 or type 2 diabetes (Sorli Cet al J *Diab Invest* 2012; 3 (Suppl. 1):196). Insulin degludec was associated with a nonsignificantly lower rate of confirmed hypoglycaemia and a significantly lower risk of nocturnal confirmed hypoglycaemia compared with insulin glargine, indicating that the advantages seen with insulin degludec in relation to hypoglycaemia are also present in the elderly. • 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). This is an advantage for many patients, for example shift workers or those dependant on others for their injections where the timing cannot be guaranteed. • The availability of the U200 formulation of insulin degludec allows patients with high dose requirements to administer the required daily dose of insulin degludec as a single injection (up to 160 IU in one injection). The delivery device for insulin degludec (FlexTouch®), has shown	

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					consistency and accuracy of dose delivery with significantly lower injection force than comparator pens (Hemmingsen H, Diabetes Technol Ther 2011; 13:1207–1211). Thus insulin degludec has an important place in therapy for patients at high risk of hypoglycaemia, those needing flexibility in dosing and those requiring high insulin doses. Novo Nordisk request that it is presented as a clear treatment option in Type 2 diabetes and incorporated into the treatment algorithm to reflect this.	
765	Novo Nordisk Ltd	Full	16	10 (Sec 1.5)	Novo Nordisk endorse the role of structured education in the treatment of type 2 diabetes.	Thank you for your feedback.
753	Novo Nordisk Ltd	Full	166	4,5,6	Decreased insulin secretion has been identified as a strong cause of Type 2 diabetes progression, therefore therapies that potentially preserve or improve insulin secretion (β-cell function) should be considered earlier in the treatment pathway. There are available clinical trials that have shown the potential positive effects of GLP-1 mimetic (liraglutide) on improving β-cell function during the treatment period of the trials. (for example, Retnakaran et al. Doi: 10.2337/dc14-0893). Novo Nordisk recommends that treatment	Thank you for your feedback. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.

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					modalities, like GLP-1 mimetic, that have shown to improve insulin secretion, provide coveted clinical benefts (such as improvements in HbA1c, weight and lipid profile) and potentially preserve β-cell function should be considered more in the treatment algorithm for type 2 diabetes management.	
771	Novo Nordisk Ltd	Full	168	42	It is stated that "RCTs containing a+(c, d or e) vs b + (c, d or e) were excluded". This has resulted in a large number of studies being excluded, with important implications for the result of the attempted at economic analyses. Attempts should be made to document the size of this impact, and reflect how the results (and potential final decisions) would differ if they had been included.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
772	Novo Nordisk Ltd	Full	169	14	It appears that combination products have been excluded from any analysis. These products have the potential to reduce the number of medications a patient requires – with positive effects on compliance. While also potentially reducing the treatment cost of some combinations. These should be incorporated.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological

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						management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
773	Novo Nordisk Ltd	Full	171	1	Third intensification, this should be discussed in more detail for patients where insulin is not considered appropriate.	Thank you for your feedback. No relevant evidence was identified at third intensification of treatment. In recognition of the lack of evidence at this intensification level, a research recommendation has been made. Given that no evidence has been reviewed for this stage of treatment, the guideline development group did not think it was appropriate to make recommendations for this phase of treatment intensification.
774	Novo Nordisk Ltd	Full	172	24	Studies were only included in the health economic model if they reported all 4 outcomes (Change in HbA_{1c}, Hypoglycaemia, Adverse events and Change in weight). For products which do not impact on weight, it is highly likely that change in weight will not be reported. And a large number of studies therefore excluded. Resulting in a large amount of relevant evidence being ignored. The implications of this decision need to be described fully.	Thank you for your feedback. All studies were included in the network meta analyses if they reported one or more outcomes; treatment options (not studies) for which all 4 outcomes were available from the network meta analyses results were included in the health economic model.
775	Novo Nordisk Ltd	Full	174	12	Using the health economic model to enforce treatment switches at specific HbA_{1c} thresholds has the potential to negatively impact the	Thank you for your feedback. Enforcing treatment switches at a given threshold is a standard practice in type 2 diabetes health

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					Economic analysis. Less effective therapies (i.e. those where HbA_{1c} does not go far below the threshold) will intensify earlier than more effective ones. If weight and hypoglycaemia were improved with the intensification treatment this could unfairly bias the results.	economic modelling. All treatment options intensified to the same treatment options. Intensification treatments (metformin-sulfonylurea, metformin-NPH insulin) are substantially more expensive than treatment options at the previous intensification level and treatment effects tend to be worse. It is unlikely that the results are unfairly biased in this way.
776	Novo Nordisk Ltd	Full	174	20	Treatment related weight losses were modelled to only last for 1 year (after which they rebounded (instantly) to their pre-trial level). This is not only a very conservative assumption (even the sensitivity analysis where the weight regain takes place over the 2nd year seems conservative), but is also inconsistent with an approach that has been accepted in a number of previous STAs. Although some weight increase could be anticipated, a weight benefit of the product should be assumed to last for the duration of its use.	Thank you for your feedback. The guideline development group discussed a variety of potential assumptions around treatment-related weight change (see appendix F 3.2.6) and was content to model treatment-related weight changes in line with the available clinical evidence for the majority of treatment options.
777	Novo Nordisk Ltd	Full	174	23	The assumption that 2% of hypoglycaemic events are severe events seems difficult to justify, and ignores the possibility that some diabetes medications have a greater impact on severe hypoglycaemia than others. The impact of this assumption needs to be extensively explored in the sensitivity analysis.	Thank you for your feedback. The limits of this assumption were noted in appendix F (3.2.7). Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been

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						based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
778	Novo Nordisk Ltd	Full	175	8	NICE should be commended for their attempt to use real world evidence do define their patient baseline characteristics. It does however seem a little confusing that the data for time to second and third intensification wasn't collected from the same data.	Thank you for your feedback. Patient baseline characteristics were taken from the same real world evidence for all intensifications, but selected at different time points to reflect the progressive nature of the disease. The time points were selected on the basis of the included randomised controlled trials and applied to the real world evidence.
745	Novo Nordisk Ltd	NICE	18	Sec. 1.6.1	The draft guideline recommends that HbA1c is measured at 3-6 month intervals (after initiating a new therapy). We would suggest the inclusion of a line 'if treatment is unsuccessful, investigate the possible reasons – and if suitable switch to an alternative'. Stopping criteria should not be exclusive to GLP-1 mimetic alone, while other non-insulin anti-diabetic agents are allowed to be continued even if they are not having a therapeutic effect. The most important part of good diabetes management is ensuring use of the right product for the right patient at the right time. There is a large degree of clinical inertia in the UK (Khunti	Thank you for your feedback. Recommendation 1.6.1 provides generic guidance on the frequency of HbA1c measurements. It states: *Measure HbA1c levels at:* *• 3–6 monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy* *• 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable. [2015]* It is beyond the remit of the recommendation to provide guidance on specific drug management. The guideline development group noted the high costs of GLP-1 mimetics and their associated

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					K et al, Diabetes Care. doi: 10.2337/dc13-0331), and this guideline should aim to address that by encouraging clinicians to assess patients regularly, and switch or intensify ineffective therapies.	stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
780	Novo Nordisk Ltd	Full	187	4	It is not clear why 'total dropouts' was included as an end-point for the NMA. While drop-outs due to Adverse Events is an acceptable proxy for patients stopping treatment. Drop-outs from a RCT for other reasons can be anticipated to be very different (moving away, trial procedures etc.) from what would be seen in a real world setting. Therefore this analysis is unnecessary, and inappropriate.	Thank you for your feedback. Where dropouts due to adverse events were not specifically reported, total dropouts provided an acceptable proxy to identify any systematic differences in acceptability of the interventions.
746	Novo Nordisk Ltd	NICE	19	1.6.5	See comment **Error! Reference source not found.** above, if a patient is unable to achieve the required glycaemic control due to hypoglycaemia, an alternative treatment (with a lower risk of hypoglycaemia) should be offered.	Thank you for your feedback. This is a generic recommendation on patient care in agreeing, setting and monitoring individual HbA1c targets. Hypoglycaemia was provided as an example of a possible adverse effect of treatment. It is beyond the remit of this recommendation to prescribe management for the specific adverse effect of hypoglycaemia.
781	Novo Nordisk Ltd	Full	192	9 – 16	The economic model predicted that patients would spend 3.4 years on initial therapy, and a further 3.1 years on first intensification therapy. This is noticeably different from the earlier assumption that patients would be intensified for the first time with a duration of diabetes of 4.5	Thank you for your feedback. The disease durations of 2 years to initial therapy, 4.5 years to first intensification and 8.5 years to second intensification were not used within the economic modelling, apart from generating patient cohorts. The durations were taken from included

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					years (cross ref p. 175). In the economic analysis, Initial therapy is started 2 years after diagnosis, first intensification occurs 4.5 years after diagnosis, and second intensification a further 4 years after that.	randomised controlled trials (RCTs) as points at which to select baseline population data from the THIN database (see appendix F 3.3 for more details). The economic model predictions of time spent on each therapy level were based HbAc1 treatment effects and profiles and intensification rules, not directly on disease duration inputs. Whilst it is acknowledged that RCT population selection does not always reflect clinical reality, the modelled treatment durations predicted that patients reached second intensification 6.5 years after starting initial treatment – the same as found in the included RCTs.
782	Novo Nordisk Ltd	Full	199	N/A	Consideration of health benefits and resource use – (here, related to pioglitazone, and throughout the guideline). There are a number of occasions in the guideline document that refer to therapies being the "cheapest". It would be more relevant to decision makers and clinicians if the text in the guideline identified the *'most cost-effective'*. It should be noted that 'cheapest' doesn't mean 'best'.	Thank you for your feedback. The text has been amended.
766	Novo Nordisk Ltd	Full	20 -22	Sec 1.5	Novo Nordisk feel that it should be clear in the recommendations that there is the option of adding insulin earlier in the treatment pathway, for example in combination with metformin, for	Thank you for your feedback. Recommendation 1.6.18 (NICE version) states that "*If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin (see*

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					appropriate patients rather than going through a series of oral drugs first.	*recommendations 1.6.31–1.6.33) or a sulfonylurea, and review treatment when blood glucose control has been achieved.*".
783	Novo Nordisk Ltd	Full	200	2-3	Out of 17,037 references – just 47 papers (relating to 34) studies were included. As a result of this the vast majority of the evidence relating to this intensification step has been dismissed – due to the strict inclusion criteria used in the systematic review. It would be beneficial to see the impact these inclusion criteria have on the studies included, (the list of excluded studies presented in appendix L is not sufficient, a modified PRISMA flow diagram showing the number of studies excluded by each criteria would be more acceptable). With a ranking of required reported outcomes (i.e. there is more justification for a study to be excluded because it doesn't report HbA_{1c} than because it doesn't report change in weight?)	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
758	Novo Nordisk Ltd	Full	219	14, 15, Appendix F Table 58	The selection criteria used in the systematic review has led to some clinical results that are not clinically logical. For example liraglutide – a product that has been extensively studied and proven to result in significant weight loss. (cross-ref table 58 in appendix F) is showing an absolute weight gain (of 0.582kg at one year), compared to a loss of 0.121kg for exenatide, when both are assessed in combination with met + su.	Thank you for your feedback. Treatment effect data were based on the results of a network meta-analysis (NMA). In the example given, one paper contributed to the NMA, in which liraglutide showed a weight change at 6 months of -1.8kg compared with insulin glargine having a weight change of +1.6kg. The NMA absolute results showed insulin glargine to have a weight change of +3.9kg and liraglutide to have a weight change of 0.6kg. Hence, the relative difference between the two treatments was maintained.
75	Novo	Full	219	14,1	It is apparent that significant quantities of	Thank you for your feedback. LEAD-2 and 1860

Type 2 diabetes (update)

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7	Nordisk Ltd			5	valuable evidence have been excluded from use within the development of this guideline. For example none of the clinical data for liraglutide use in dual therapy (first line intensification) is considered (in the NICE technology appraisal for liraglutide [TA203], three trials (LEAD-1, 1860 and LEAD-2) were strongly considered for a dual therapy (first line intensification) recommendation). Subsequently the decisions detailed within the guideline are informed by only a small subset of the available evidence. This approach should be reconsidered.	have been included in the review in the guideline. LEAD-1 was excluded because it compared across treatment strategies i.e. liraglutide+sulfonylurea vs. sulfonylurea+placebo and as rosiglitazone is an exclusion criterion for the review, the combination rosiglitazone+sulfonylurea was not considered.
784	Novo Nordisk Ltd	Full	220	18 - 23	The text implies metformin + DPP-4 inhibitor is as effective as metformin + GLP-1 mimetic, whereas the results of the NMA (P215) show that GLP-1 + metformin is better for both HbA_{1c} and weight, so it would be appropriate for GLP-1 to be mentioned first on line 19.	Thank you for your feedback.
767	Novo Nordisk Ltd	Full	23	27 (Sec 1.5)	Novo Nordisk agree with considering those on basal insulin or premix insulin for commencement of short acting insulin before meals. However, the advantages of short acting analogue insulins over human insulin should be highlighted in terms of improved postprandial control, reduced hypoglycaemia and ability to inject immediately before or soon after a meal.	Thank you for your feedback. The last bullet in recommendation 1.6.33 (NICE version) provides circumstances when short-acting insulin analogues should be considered and includes those listed.
747	Novo Nordisk Ltd	NICE	25	1.6.29	Combination therapy with a GLP-1 is recommended as an option for patients who are obese. The threshold for obesity should be	Thank you for your feedback. The health economic literature review found 1 partially applicable paper with potentially serious

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					>30kg/m2. There is evidence for the cost-effectiveness of liraglutide in this population. It should also be clarified that appropriate adjustment is required for non-caucasians.	limitations that covered liraglutide (see full guideline 8.4.9.1). As no directly applicable studies with only minor limitations were found that covered all the comparators under consideration for each sub-question for this guideline, an original economic analysis was undertaken. The guideline development group did not consider any sub-groups of the clinical evidence that would have allowed such groups to be modelled in the cost-effectiveness analysis. Consideration for adjusting BMI levels based on ethnicity has been carried forward from CG87 recommendation.
787	Novo Nordisk Ltd	Full	252		In the 'Quality of the evidence' section it states that the GDG highlighted that patients with early type 2 diabetes are more likely to be using long acting insulin. However according to the health economic modelling, insulin is not a treatment option until the second intensification (When patients are reported to have been diagnosed for > 8 years).	Thank you for your feedback. When modelling second intensification, the health economic modelling fully probabilistically sampled baseline characteristics. Therefore, the health economic modelling will have included some younger people who reach second intensification with short disease duration.
768	Novo Nordisk Ltd	Full	255	Sec 8.4.17.3	As per above, Novo Nordisk feel that it should be clear in the recommendations that there is the option of adding insulin earlier in the treatment pathway, for example in combination with metformin, for appropriate patients rather than going through a series of oral drugs first.	**Thank you for your feedback. Recommendation 1.6.18 (NICE version) states that "*If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin (see recommendations 1.6.31–1.6.33) or a sulfonylurea, and review treatment when blood glucose control has been achieved.*"**

Type 2 diabetes (update)

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769	Novo Nordisk Ltd	Full	255 -257	Sec 8.4.17.5	Novo Nordisk feel there should be a clear recommendation for insulin degludec to be used in patient populations who are at high risk of hypoglycaemia, those needing flexibility in dosing and those requiring high insulin doses as per above comment. Novo Nordisk feels this should be presented as a clear treatment option in Type 2 diabetes and incorporated into the treatment algorithm to reflect this.	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec–metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec–metformin, and subsequently it does not appear in the algorithm.
770	Novo Nordisk Ltd	Full	255-257	Sec 8.4.17.5	Novo Nordisk agree with considering those on basal insulin or premix insulin for commencement of short acting insulin before meals. However, we feel that the advantages of short acting analogue insulins over human insulin should be highlighted in terms of improved postprandial control, reduced hypoglycaemia and ability to inject immediately before a meal.	Thank you for your feedback. The last bullet in recommendation 1.6.33 (NICE version) provides circumstances when short-acting insulin analogues should be considered and includes those listed.
752	Novo Nordisk Ltd	Full	257	15,16,17	In the draft guideline, NICE have made a recommendation that: *"If more than 1 option is considered appropriate for the person, choose the GLP-1 mimetic with the lowest acquisition cost".* There is no evidence to this recommendation.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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					With DPP4i, a rationale was made to the recommendation of choosing the DPP4i with the lowest acquisition cost. There doesn't seem to be any such discussions or rationale awarded for GLP-1 RAs. Therefore, how has this recommendation been substantiated? In a clinical setting, prescribers and HCPs should not focus on financial factors in their management plans for clinical excellence. A focus on lowest acquisition cost may be perceived as not prioritizing patient outcome (e.g. target HbA_{1c}) as the ultimate endpoint. If there is more than one clinically suitable option for GLP-1 mimetic, decision-making should be governed by patient-centric factors like clinical effectiveness (glycaemic control and weight loss), patient preference (number of daily injections), responder rates and safety profile of the medicine, and not just price. This is particularly relevant considering that the systematic review, and health economic modelling performed as part of this guideline did not include all of the GLP1, and the recommendations contained within are based on limited evidence for exenatide and liraglutide only.	The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
760	Novo Nordisk	Full	257	15,16,17	The GLP-1 RAs considered for second intensification analysis were liraglutide and	Thank you for your feedback. The guideline development group has reflected on the clinical

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	Ltd				exenatide. It seems inappropriate to make a broad recommendation on a class of products where evidence-based analysis was sourced from only two products within that class. Novo Nordisk recommends that NICE should specify the particular GLP-1 RAs to be considered at second line intensification, based on clinical evidence provided and used at that level of analysis.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
756	Novo Nordisk Ltd	Full	257	18,19,20	The concept of stopping criteria for GLP-1 should be applied to all glucose lowering agents after a specified period of time to ensure that they are effective. Stopping criteria should not be exclusive to GLP-1 mimetic alone, while other non-insulin anti-diabetic agents are allowed to be continued even if they are not having a therapeutic effect. The most important part of good diabetes management is ensuring use of the right product	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.

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					for the right patient at the right time. There is a large degree of clinical inertia in the UK (Khunti K et al, Diabetes Care. doi: 10.2337/dc13-0331), and this guideline should aim to address that by encouraging clinicians to assess patients regularly, and switch or intensify ineffective therapies.	
754	Novo Nordisk Ltd	Full	257	7,8	Novo Nordisk suggest that GLP-1 mimetics should also be considered in type 2 diabetic patients that meet criteria for obesity. Based on WHO classification, BMI ≥30 is considered as a definition for obesity. Therefore, BMI ≥30 should be considered as the initial BMI threshold for initiating GLP-1 RAs, rather than ≥35. Many national bodies with an interest in weight management (National Institution for Health; European Association for the Study of Obesity; Scottish Intercollegiate Guidelines Network) respect the clinical significance of BMI ≥30 as an isolated risk factor for considering intensive weight control. Furthermore, a BMI ≥35, in isolation, should be a suitable enough indication for considering weight control in diabetes management. There should not be a need for "**and** specific psychological and other medical problems related with obesity". In addition, this recommendation does not take	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Consideration for adjusting BMI levels based on ethnicity has been carried forward from CG87 recommendation.

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					account of the fact that different BMI cut-offs should be considered for alternative ethnicities.	
788	Novo Nordisk Ltd	Full	258	1	For patients already using an insulin analogue, and still having problems with recurrent hypoglycaemia, a trial of insulin degludec should be a treatment option.	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec-metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec-metformin, and subsequently it does not appear in the algorithm.
755	Novo Nordisk Ltd	Full	259	22,23	Studies including GLP-1 RA and insulin do exist, but not in early phase of treatment. These later phase studies should be taken into consideration.	Thank you for your feedback. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics in combination with basal insulin at any point in the care pathway were not identified at the cut off search date of June 2014. Any studies published after this date could not be included in this update. Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the

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						revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
748	Novo Nordisk Ltd	NICE	27	1.6.34	We would suggest that, if a patient experiences problematic hypoglycaemia despite using a long acting insulin analogue (insulin detemir, insulin glargine), consider using insulin degludec, a product with a lower rate of hypoglycaemia..(insulin degludec SmPC, Table 2, p. 9)	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec–metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec–metformin, and subsequently it does not appear in the algorithm.
789	Novo Nordisk Ltd	Appendix F	27	Section 3.2.1	Intensification was assumed to occur at HbA_{1c} = 7.5, however while this is a reasonable target – it is a long way from the current reality. Khunti K et al. (Diabetes Care November, 2013. (36) 11 3411-3417) reported a mean HbA1c of 8.8% in patients taking 2 OADs, and is therefore unrealistic.	Thank you for your feedback. The guideline development group was happy to use 7.5% as level at which treatment should be intensified

Type 2 diabetes (update)

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790	Novo Nordisk Ltd	Appendix F	27	Section 3.2.1	Treatment effects such as SBP and cholesterol l were not incorporated in the economic model. However products such as GLP-1 mimetics have positive effects on SBP and cholesterol. By not capturing these effects – the health economic modelling conducted is under valuing these products.	Thank you for your feedback. The guideline development group did not prioritise these clinical outcomes for these review questions.
743	Novo Nordisk Ltd	NICE	5	general	It is noted that care should be centred around the patient, and that "Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals". However we are disappointed that that sentiment is not reflected in the guideline, especially the treatment algorithm. Novo Nordisk would encourage a more patient focussed treatment algorithm.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
791	Novo Nordisk Ltd	Appendix F	53	Section 3.5.1	The results for change in HbA_{1c} are adjusted for baseline HbA_{1c} for use in the health economic model to an assumed baseline level of 7.5%.	Thank you for your feedback. HbA1c level of 7.5% was not used as an assumed baseline, but as a regression centring point. Any value could

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					This has the effect of minimising the clinical (HbA_{1c} lowering) effect of all of the therapies (and subsequently minimising the differences between them). This does not reflect the reality of clinical practice, where patients are switched with an HbA1c level that is often higher than that in the RCTs where the true efficacy is seen. As mentioned in comment **Error! Reference source not found.** people with diabetes in the UK are not all switching treatment at an HbA1c of 7.5%, the patients seen in the majority of clinical trials (where the mean HbA1c is often around 8.5%) are more representative of the real clinical situation. It is noted that similar adjustments were not made for the rate of hypoglycaemia (in general, as HbA_{1c} decreases, the rate of hypoglycaemia should be expected to increase accordingly). Once again potentially biasing the results of the analysis by not disadvantaging those therapies that increase the rate of hypoglycaemia.	have been selected as a centring point and the results would have converged to the same answer. However, the use of a value close to the mean of the distribution was computationally efficient. Each model used the baseline data to generate a heterogeneous population.
792	Novo Nordisk Ltd	Appendix F	82		Costs were taken from the UKPDS publication, and inflated to 2013. However a better approach could have been to perform a systematic review to identify the treatment costs associated with each complication, according to more recent practice.	Thank you for your feedback. The benefit of sourcing long-term complication event rates, costs and utilities from the same randomised controlled trial was considered to outweigh the benefit of using alternative cost sources where the definitions of events may not have matched the particular ones used in UKPDS.
79	Novo	Appendi	88		It is noted in table 65 that all use of NPH is	Thank you for your feedback. In appendix F,

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3	Nordisk Ltd	x F			assumed to be once-daily. The costs for twice-daily administration of NPH should at least be considered. Unless the assumption is that any patient who needs NPH more than once daily will be switched to a basal insulin analogue.	table 65 indicates that use of NPH insulin varies between once and twice daily, depending on the treatment option. Table 68 shows the average daily doses of NPH insulin for all treatment combinations, which match daily injections in table 65.
794	Novo Nordisk Ltd	Appendix F	93		The daily dose of NPH insulin (when NPH insulin is used in the absence of OADs) is in excess of the maximum afforded by the injection devices that it is supplied in. Subsequently this would have to be injected twice. This will incur additional costs that should be included.	Thank you for your feedback. In appendix F, table 65 indicates that use of NPH insulin varies between once and twice daily, depending on the treatment option. Table 68 shows the average daily doses of NPH insulin for all treatment combinations, which match daily injections in table 65.
795	Novo Nordisk Ltd	Appendix F	97 - 99		It is noted that the disutility applied for hypoglycaemic events was the same as that used in the previous (2008, 2009) guidelines. A recent systematic review (Beaudet et al. 2014) is referred to; however that published review only includes searches up to May 2012. Additional evidence (including Evans et al. Health and Quality of Life Outcomes 2013, 11:90 – doi: 10.1186/1477-7525-11-90) which includes data on UK patients, exists on the impact of hypoglycaemic events. This evidence should be considered	Thank you for your feedback. Whilst the same source of hypoglycaemic episode disutility was used as in previous guidelines, it was applied differently to previous guidelines. The paper referenced did not provide a multivariate analysis and was not specific to this country.
796	Novo Nordisk Ltd	Appendix F	98		We note with interest that the GDG decided to give nocturnal events of hypoglycaemia their lowest priority. However feedback from patients suggests that nocturnal hypoglycaemia is the type of hypoglycaemia that has the greatest impact on patients and their families (Brod 2009,	Thank you for your feedback. The guideline development group (including representatives of people with type 2 diabetes) were happy with their prioritisation of hypoglycaemic episodes.

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					doi:10.1016/j.jval.2011.02.001) (the results form Evans et al. 2013 [doi: 10.1186/1477-7525-11-90] reflect that). This needs to be rectified.	
785	Novo Nordisk Ltd	Full	General (section 8.4)		There are a number of inclusion criteria used in the systematic review that result in some treatments being completely excluded (e.g. lixisenatide). However some of the recommendations are based on the class level. Therapies that have not been assessed should not be (implicitly or explicitly) included in the recommendations. Especially where it is known that there are large differences in the clinical effects of the products.	Thank you for your feedback. Treatments were only grouped as classes where the guideline development group (GDG) believed that there were no material differences in effect between the individual class members (see Linking Evidence to Recommendations tables, section 8.4.7, 8.4.11 and 8.4.15). For GLP-1 mimetics, there was no evidence that any of the members of this class could routinely be used as effective and cost effective options in the control of blood glucose. However, the GDG wished to maintain recommendations allowing their trial use in situations where the patient might derive particular benefit. Since these recommendations were not directly based on relevant evidence, but relied more on the GDG's knowledge and experience, there was no reason to restrict them to 1 or more particular product. Therefore, the GDG concluded it was reasonable to refer to GLP-1 mimetics as a class. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of

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						drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
786	Novo Nordisk Ltd	Full	General (section 8.4.12)		In clinical trials involving insulin, it is important to assess the contribution of different insulin doses. The majority of (if not all) studies involving insulin have been conducted under treat-to-target' principles. Subsequently (dependent on the actual target specified) the effect on HbA_{1c} is generally the same. But differences will be noticed in other parameters such as hypoglycaemia. Failure to account for the different dosing and hypoglycaemia rates in the NMA will make these results largely uninterpretable.	Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.
742	Novo Nordisk Ltd	NICE	General	General	Novo Nordisk would like to take this opportunity to thank NICE on developing the *draft* Type 2 Diabetes Mellitus clinical guidelines since it is of course a huge task given the plethora of clinical and economic evidence available for anti-diabetes treatments. The most important goal in terms of treatment	Thank you for your feedback.

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					for people with Type 2 diabetes is to reduce HbA_{1c} to target levels to prevent long-term micro- and macro-vascular complications. Hypoglycaemia remains an adverse-effect of some anti-diabetes treatments but this is minimised to certain degrees depending on the treatment chosen, as does weight-gain and in fact a weight-loss benefit with some. These are important factors to consider and should be taken into consideration alongside patient preferences when selecting an appropriate treatment. 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, and where necessary real-world evidence should also be considered as to better inform decision makers ultimately for the benefit of the patient. In our response we commend your efforts 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.	
75	Novo	Full	Gene	gene	Blood glucose management : Clinical practice is	Thank you for your feedback.

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9	Nordisk Ltd		ral	ral	rightly governed by clinical-based evidence. However, novel therapy will persistently receive prudent recommendations because older well established therapies are currently heavily recommended and used more readily in real world and at baseline in clinical trials. Therefore, novel therapies will continue to be unfairly represented in pooled meta-analyses.	
761	Novo Nordisk Ltd	Full	General	general	Novo Nordisk have concerns about the positioning of pioglitazaone within the guideline as a first line treatment, given the proven increased risk of bladder cancer. We suggest the EMA considerations and restrictions of use for pioglitazone are incorporated into the guideline accordingly. MHRA Drug Safety Update 2011 - https://www.gov.uk/drug-safety-update/pioglitazone-risk-of-bladder-cancer EMA Press Release 21-07-2011 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001311.jsp&mid=WC0b01ac058004d5c1	Thank you for your feedback. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
511	Nuffield Department of Population Health	Full	94	10	Effect of adverse effects of aspirin on quality of life. Aspirin use is associated with an increased risk of both intracranial and extra-cranial (mostly gastrointestinal) haemorrhage, and other	Thank you for your feedback and information regarding the increased absolute risk of bleeding in people with diabetes compared to those without diabetes.

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					gastrointestinal complications. In 6 trials assessing aspirin as primary prevention for cardiovascular disease in the 2009 ATT analysis, allocation to aspirin resulted in 54% (relative risk 1.54 [95% CI 1.30-1.82]) relative increase in the risk of major extra-cranial bleeding and a 32% (relative risk 1.32 [95% CI 1.00-1.75]) relative increase in intracranial bleeding, although most of the individuals in those trials did not have diabetes. However, in this ATT analysis of primary prevention trials, the absolute risk of bleeding was increased by around 50% among individuals with diabetes compared to those without diabetes.[1] The GDC considered that *"any bleeding events would have a large negative impact on a patient's quality of life and anxiety levels"* but there is a lack of data to support this. Further evidence is needed to assess the impact of these events on quality of life among people with diabetes. In ASCEND we are measuring quality of life using the EQ-5D questionnaire which will generate useful data to help assess the disutility associated with these outcomes along with the vascular outcomes studied. This will inform health economic analysis using diabetes specific effect size, directly assessed disutility and diabetes specific bleeding rates (not used in Lamotte et al 2006). Again, highlighting the need for these data will help to ensure the success of the study.	

Type 2 diabetes (update)

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512	Nuffield Department of Population Health	Full	95	General	The GDC expressed concern that the results of some trials might not be generalizable to the UK diabetic population because the baseline HbA1c was only 53 mmol/l [7%]), however, data extracted from the Clinical Practice Research Datalink (CPRD) shows that the mean HbA1c among around 36,000 people with type 2 diabetes in the UK is indeed 7%.[4] It would be important to incorporate HbA1c along with other prognostic factors to identify a population who may benefit from antiplatelet treatment.	Thank you for your feedback. The cited CPRD dataset was on newly diagnosed patients with type 2 diabetes and therefore, unsurprisingly the mean HbA1c value was low at 7%. It may be useful to identify patients who would benefit from antiplatelet treatment for the primary prevention of cardiovascular disease such as those with microalbuminuria and this has been highlighted in the Linking Evidence to Recommendation table in section 7.2 in the full guideline.
510	Nuffield Department of Population Health	Full	97	2 -8	<u>No research recommendation for statement 30 and 31</u> We agree with the recommendation not to offer antiplatelet therapy to adults with type 2 diabetes who do not have a history of cardiovascular disease, since there is currently insufficient evidence of benefit and a genuine concern about harm. However, by making no research recommendations in relation to this review question these guidelines give the impression that this research question has been reliably answered. The ASCEND trial, conducted by the Clinical Trial Service Unit (CTSU) in the Nuffield Department of Health (NDPH), University of Oxford has completed approximately 5 years of the planned 7.5 year follow-up (which will be supported by an further British Heart Foundation Special Project Grant awarded in 2014). At this point in the study our main challenge is to maintain adherence to	Thank you for your feedback. In the full guideline, the importance of ongoing trials (ASCEND, ACCEPT-D) in providing more direct and applicable evidence to determine whether antiplatelet therapy is effective in primary prevention of cardiovascular disease in people with type 2 diabetes and relevant subgroups has been highlighted. The guideline development group did not consider it necessary to make further research recommendations in this area.

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					study treatment. We are concerned that participants, and their doctors, might see these guidelines as a reason to stop their study treatment, making it more difficult to obtain reliable evidence. The Anti-Thrombotic Trialist Collaboration (ATT), co-ordinated from within CTSU, includes individual patient data from those with diabetes in 6 primary prevention trials, along with ETDRS, JPAD, POPADAD and those with diabetes in the Aspirin for Asymptomatic Atherosclerosis study and the Japanese Primary Prevention study. Together these data include around 1400 major vascular events of which over 500 events occurred in the ETDRS trial, which was conducted before modern cardiovascular prevention was routinely used.[1] There is, therefore, relatively little information about the possible beneficial effects and potential harms of aspirin among people with diabetes. The GDC was *"confident that aspirin would not be of sufficient benefit for the majority of patients with type 2 diabetes who had not previously experienced a cardiovascular event".* Among low risk individuals any potential benefit of aspirin on cardiovascular events is likely to be accompanied by a similar increase in the risk of bleeding.[1] However, in populations with moderate cardiovascular risk (such as those with diabetes) the balance between benefit and	

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					harm requires careful assessment. In the ATT, around 4000 of the 95,000 participants in the 6 primary prevention trials reported diabetes at baseline. Among these individuals, aspirin was associated with a 12% relative reduction in major vascular events (relative risk 0.88 [95% CI 0.67-0.15]).[2] However, given the rates of major vascular events in these patients (1.87% per year in the control group) this would translate into only 2 or 3 major vascular events avoided per 1000 people treated per year.[2] Assessment of the balance of benefit and harm in those with diabetes will require a reliable estimate of the proportional effects on both cardiovascular disease and bleeding events along with careful consideration of the absolute rates of these conditions. The results of ASCEND and ACCEPT-D will help to address this question. Even if aspirin were not worthwhile for patients with diabetes overall, it would be important to identify a group of individuals with diabetes at higher risk who may benefit from antiplatelet treatment. For example, in the Third National Health and Nutrition Estimation Survey (NHANES III) in the US around 40% of individuals with type 2 diabetes had "kidney disease" (defined as albumin/creatinine ratio >30 mg/g or an eGFR <60 ml/min/1.73m^2). The cumulative 10 year cardiovascular mortality rate among these individuals was 20% compared to only 7% among those with diabetes but no	

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					kidney disease.[3] Because the risk factors for bleeding are similar to the risk to the risk factors for cardiovascular disease[1], it is not possible to simply apply the overall estimate of the effect of aspirin on the cardiovascular disease rates in higher risk groups. However, individual patient data meta-analysis of the available data from completed trials, data from current trials in diabetes such as ASCEND and ACCEPT-D and individuals with diabetes from other ongoing studies such as ASPREE could be used to try and identify a group of people with diabetes, but without known cardiovascular disease, in whom the benefit from aspirin may outweigh the risk. To help ensure the success of these studies we request that the need for additional randomized evidence on the effects of aspirin (or other antiplatelet agents) among individuals with diabetes but no prior cardiovascular disease, and the need for careful meta-analysis of these data, is highlighted in this guideline.	
220	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	12 11 16	1 -4 3-4	These lines, recommending target-setting, are in contradiction to, and render meaningless, the individualised approach recommended in lines 33-34 of Pg 11 or lines 3-4 of Pg 16. In our experience a generic target based approach is not appropriate for managing patients with type 2 diabetes. The proposed HbA1c target of < 7.5%) has been selected as a compromise from epidemiological analyses, since there is no RCT	Thank you for your feedback. The recommendation provides a drug intensification threshold of 58 mmol/mol (7.5%) with an associated target set at 53 mmol/mol (7%). A drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) was not selected as it was considered too low and inappropriate for most people as the condition progresses. While the guideline development group recognises that

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					evidence base. We do not believe that one target can be appropriate for all people, and, even allowing for the caveat in the footnote 1 of the diagrams, we believe that a generic target is misguided. This target of <7.5% is reproduced *25 times* in the three diagrams. Our view would be that targets should be at or near 6.5% for those early in the disease process and modified according to other principles outlined in the ADA/EASD guidelines. Later in the disease process 7.5% HbA1c may be too low - the old and infirm often need to have higher targets. There should be proper discussion of the criteria by which these targets are set. *(Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012 Jun;55(6):1577-96.* *Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Jan 13.).*	there may be circumstances where the recommended targets are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE version), judicious aspirational targets are important in guiding quality patient care. The guideline's target recommendations (see recommendations 1.6.5 to 1.6.11) encompass the scenarios mentioned in your comment. Recommendation 1.6.7 suggests setting a target of 48 mmol/mol (6.5%) for people who are managed by lifestyle/diet or in combination with one oral drug not associated with hypoglycaemia. This group of individuals would typically fall in the category of those early in the disease process. Recommendation 1.6.9 suggests relaxing the HbA1c target on a case by case basis considering the frail or elderly among other factors.

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221	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	12	14 -15	The issue here is about the likelihood of information being gained and therapy being changed. Self-monitoring is extremely helpful to those beginning treatment to asses the effects of food, alcohol, over-indulgence, diurnal variation, hypoglycaemia and exercise. Secondly, monitoring is useful to assess the effects of therapeutic interventions. While therapy is being altered or changed both patients and physicians use such data to inform and modify the process. That a randomised trial showed little effects on HbA1c is not relevant since patients in that trial were not selected on the two major criteria of recent onset or therapeutic manoeuvring (*Farmer A, et al. [2007] Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 335: 132*.) The recommendation about using self-monitoring in patients on exogenous steroids is strange and ignores several clinical conditions (e.g. Infections) where endogenous steroid levels may be high with similar consequence on blood glucose levels.	Thank you for your feedback. Self-monitoring of blood glucose levels (SMBG) is aimed at improving glycaemic control and should therefore influence HbA1c levels. The evidence review included studies that comprised individuals on diet/lifestyle, oral antihyperglycaemic drugs and insulin. Subgroup analyses based on the individuals' therapeutic management showed no clinically meaningful improvement in HbA1c in people on diet and/or oral drugs or people on diet, oral drugs and/or insulin (see Appendix D for forest plots). No studies that looked at the effectiveness of SMBG in people with type 2 diabetes and acute intercurrent illnesses was identified and therefore the guideline development group has made a research recommendation.
222	Oxford Centre For Diabetes, Endocrinology and Metabolis	Full	13	2 -3	Repaglinide is an odd choice of therapy for those failing on metformin. The evidence-base for repaglinide is miniscule and the fact that it needs to be taken three times daily simply ignored. There are no substantive data for its use as first-line therapy in the event of	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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	m				metformin failure, nor has repaglinide been used in comparator arms of trials because it is not in routine use. Unlike most other agents used there is no major outcome trial and no CVD trial. This therapeutic suggestion runs counter to any previously assembled guidelines on the subject - the only justification being on the basis of being sulfonylurea-like with a lack of hypoglycaemia (see also 9 below). A predominant view was that NICE would lose credibility if this were seriously proposed as the first choice in metformin failure. That it emerged from modelling shows the extent to which modelling can lose contact with the therapeutic realities. If the modelling is based on the occurrence of hypoglycaemia, then this too is flawed. Glibenclamide is cheap and *does* cause hypoglycaemia, but few prescribe this now. Gliclazide is more expensive but causes little in the way of hypoglycaemia and, crucially, is the subject of a large outcome trial. *(The ADVANCE trial. Patel A et al. Lancet 2007;370:829-840)* Repaglinide is rarely the comparator arm of any outcome trial. The reason for this is: a. Repaglinide would not be seen as a useful comparator - since it is so rarely used b. Repaglinide is never mandated as a comparator in FDA or EMA trials – again since it is so rarely used c. Repaglinide needs to be taken three times daily and therefore compliance becomes a	recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The ADVANCE trial has been excluded from the review because all participants were on various pre-existing therapies.

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					major issue.	
223	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	13	2 -3	The evidence-base for pioglitazone in metformin failure is also small. Pioglitazone caused an increase in heart failure in the ProActive trial and causes significant weight increase. *(Dormandy JA, et al PROspective pioglitAzone Clinical Trial In macroVascular Events: a randomised controlled trial. Lancet 2005;366:1279-1289)* That rosiglitazone was withdrawn for a while from the market-place shows the extent to which the PPARy agonists should be used with caution. Most newly diagnosed T2DM patients are overweight and to prescribe, early, an agent that is known to cause significant weight increase is therapeutically inappropriate and unlikely to be appreciated by patients.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Although the PROActive trial was excluded from the long-term safety review (section 8.5 of the full guideline), the guideline development group considered that serious adverse effects would be identified in the MHRA safety alerts. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added.
224	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	13	2 -3	The figures looks like circuit diagrams. They are highly repetitious - what is the point of duplicating the lowest set of diamonds four times? The content is identical.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased

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						emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
225	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	14 -15	1	These figures are unlikely to gain any tractability - they are based on nodal points unlikely to be used in clinical practice. The consistent and (insistent x25) use of HbA1c of 7.5% is unhelpful even when there is a footnote 1 (see point 1 above)	Thank you for your feedback. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
226	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	15	1	The box on this figure states 'SGLT2 inhibitors may be appropriate for come patients but are beyond the scope of this guideline' Why beyond the scope? The document runs to 342 pages, yet a widely used, efficacious oral therapy with two products on the formulary and in clinical outcome trials, with more in the pipeline is apparently 'beyond the scope'! There are technology appraisals in place, outcome trials reported for safety and thousands of patient-years experience. If the ADA and EASD can update their guideline this year (see point 1 above) on the basis of their wide availability it is simply not acceptable for these agents not to be assessed.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
229	Oxford Centre For Diabetes, Endocrinology and Metabolis	Full	168	30-33	An admission of a negligible evidence-base for using repaglinide in metformin failures.	Thank you for your feedback. Generally, there is a dearth of studies specifically in people who are contraindicated or cannot tolerate metformin.

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227	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	22	37 -39	It is disappointing to note that the recommendation regarding discontinuing GLP1 agonists in patients who meet both criteria for reduction in HbA1C and weight loss is being retained in the new guidance. In clinical experience some patients have significant reduction in HbA1C with modest or no weight loss – it is not reasonable to discontinue / change treatment in this group of patients. Equally, prevention of an inexorable rise in HbA1c and/or weight is still a clinically relevant treatment goal which NICE should acknowledge. Long acting GLP1 agonists have considerable clinical trial data and may be appropriate for some patients – they have not been considered in this guidance.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
228	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	240	1-3	The network meta-analyses demonstrate little of clinical relevance, since they can only seek to finesse published trial findings. Trials, particularly those performed for regulatory purposes, are often undertaken in specific populations that are almost always non-comparable (in duration of diabetes, recruitment HbA1c, race, demographics etc) to routine clinical practice. Trials report median results that do not take into account the variability of response in a heterogeneous disease like diabetes. They do however highlight the extent to which some combinations are more studied than others - and here circles 19 and 24	Thank you for your feedback. Research evidence is used to make population level recommendations in clinical guidelines.

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					illustrate the paucity of data we have on repaglinide (see point 3 above).	
236	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	8.5.2.2		There *is* an outcome trial for pioglitazone: Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-1289	Thank you for your feedback. The guideline development group is aware of the PROActive trial (see LETR table section 8.5.4 in full guideline) which was excluded from the review as participants' pre-existing therapy was unclear. The guideline development group noted the need to consider MHRA safety advice when discussing the risks and benefits of treatment options with people with type 2 diabetes.
230	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		The evidence base, beyond Metformin, does not allow a hierarchy of choice in second and third-line therapies. This is outlined in the ADA/EASD position statement. *(Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015 Jan;38(1):140-9)* The Association of Physicians in the USA *(Qaseem A et al.. Ann Intern Med 156: 218-31)* adopted a strict evidence base approach and	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.The recommendations and algorithm have also been

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					concluded: *RECOMMENDATION 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence). RECOMMENDATION 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence). RECOMMENDATION 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).* We agree. Beyond metformin there is no comprehensive head-to-head comparative data that allows one to conclude that a is better than b (or c or d). What one can do is to adduce evidence from those who use these agents in clinical practice and from trials as to their relative advantages and disadvantages. These include efficacy, weight-gain, hypoglycaemia, side effects and cost. We believe that one should be more inclined to use those agents where CV outcome trials are published (SUs, insulin, metformin, pioglitazone, DPP4i) rather	simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					than those where no such data exist (repaglinide). We believe that obesity is a significant precipitating factor for type 2 diabetes, and therefore agents that cause weight increase (SUs, pioglitazone, insulin) should be used with caution early on, while those that are weight neutral (DPP4i, metformin) or weight reducing (SGLT2i and GLP-1 agonists) might be more appropriate. To construct a hierarchy on the basis of a model loses touch with reality. Clinicians deal with patients, not with models.	
231	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		Hypoglycaemia is a significant cause of comorbidity, so agents that do not cause hypoglycaemia (GLP1 agonists, DPP4 inhibitors, SGLT2 inhibitors) could be used especially in the elderly or frail or where hypoglycaemia can have catastrophic and life threatening sequelae.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are

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						appropriate, choose the option with the lowest acquisition cost).
232	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		The algorithmic approach with nodal points belies the clinical complexity of therapeutic choice and that this will have significant impact on health care in the UK by mandating unusual and unsuitable treatment in many patients.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
233	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		By adopting a position so far from the main-stream evidence base (UKPDS for initial therapy; MACE outcome trials for secondary therapy and beyond), it seems likely that NICE will be seen as being more concerned with cost than with effectiveness or safety.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been

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						simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
234	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		The multiplicity of network analyses where only a 'modelled' conclusion can be drawn gives the reader the impression that much work has been undertaken, but too little thought applied to the clinical realities.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
235	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		The ADA/EASD update discussed the emerging option of using a GLP-1 agonist in combination with basal insulin as the final common pathway in progressive beta-cell failure. This aspect is completely ignored in this NICE guideline. There can be no justification for not considering this appropriate evidence-based therapy in a 342 page document.	Thank you for your feedback. This issue was recognised by the guideline development group who made a research recommendation on the early use of insulin and GLP-1 mimetics (see full guideline section 8.4.18).
237	Oxford Centre For Diabetes, Endocrinology and Metabolism	Full	General		We noted with some concern that, on the committee, there was a minority of physicians with appropriate expertise in prescribing therapy for T2 diabetes. Whilst applauding the anti-duality stance of NICE, we do nevertheless think that including more of those with an in-depth practical experience of treating T2 diabetes	Thank you for your feedback. The constituency of the guideline development group was agreed following the stakeholder workshop during the scoping of the guideline. Members on the group were recruited via open advert, with a shortlisting and interview process. The guideline development group on this iteration of the

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					might have been advantageous.	guideline included an additional diabetologist (3 in total compared to 2 in the group for clinical guideline 66), 2 pharmacists, a nurse and 2 GPs, one with a strong academic background. NICE is confident that the committee included healthcare professionals with appropriate expertise in prescribing.
581	Oxfordshire CCG	NICE	11	33	Despite there being a footnote the HbA1C target is more prescriptive within the algorithm than within the text. GPs may be more likely to use the algorithm as a quick reference than the text and therefore set Hb1Ac targets which are inappropriate for the patient.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
580	Oxfordshire CCG	NICE	13	General	The algorithm is difficult to follow and will not translate easily and clearly on GP computer systems.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

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588	Oxfordshire CCG	Full	167	20 -26	The treatment comparisons are at odds with page 166 line 21 which says 'that augmenting existing drug treatment with additional medicines will provide glycaemic control'. Whereas page 167 line 20-26 the sub review questions may have led to repaglinide as the favoured option contrary to page 166.	Thank you for your feedback. "Augmenting existing drug treatment with additional medicines" refers to adding other drugs when the initial drug treatment(s) no longer continues to control HbA1c levels (termed "intensification" in the guideline). Treatment options at initial therapy, first and second intensification were mutually exclusive. No comparisons of treatment options across different intensification levels were made, for example, initial therapy drug options were not compared first intensification treatment options.
584	Oxfordshire CCG	Full	168	11-15	Although the GDG noted that there is a cycling through monotherapy in some conditions, in many conditions eg hypertension, asthma, pain you do not cycling through monotherpay but additional medication is provided. We therefore think that the GDG assumption is inappropriate.	Thank you for your feedback. This assumption may be equally valid in the list of conditions provided.
589	Oxfordshire CCG	Full	172	24	There is nothing in the critical outcomes about cardiac outcomes or any major events. This is an important consideration in diabetes care.	Thank you for your feedback. The guideline development group reviewed the long-term serious adverse effects of blood glucose lowering therapies as part of section 8.5 in the full guideline. The guideline development group considered long-term risk evidence alongside clinical and cost effectiveness and noted the need to consider MHRA safety advice when discussing the risks and benefits of treatment options with people with type 2 diabetes.
591	Oxfordshire CCG	Full	179	6	This chart shows that there is no significant difference (due to wide 95% confidence	Thank you for your feedback. The credible intervals are generally wide and as a result, there

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					intervals) between repaglinide, modified release sulfonylurea, standard sulfonylurea, pioglitazone for HbA1C at 3 6 and 12 months.	is considerable overlap amongst the 4 listed drugs. The guideline development group has reflected on all the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
590	Oxfordshire CCG	Full	183	1	There is no data for repaglinide in table 49 and figure 13.	Thank you for your feedback. Data on repaglinide are represented in Table 49 which shows rankings of treatment options for Change in HbA1c at 12 months. Figure 13 does not include repaglinide data at Change in HbA1c at 24 months.
585	Oxfordshire CCG	Full	198	General	The GDG did not seem to take into account that with a major change in current practice in using a drug that has a low familiarity and which cannot have another drug added to it that there is a danger in practice that another drug will in fact be prescribed as an addition ie repaglinide will be used outside of license.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where

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						metformin is contraindicated or not tolerated. In addition, recommendations referring to repaglinide make clear in footnotes that "Repaglinide has a marketing authorisation for use only as monotherapy or in combination with metformin. Therefore, for people who cannot take metformin, there is no licensed combination containing repaglinide that can be offered at first intensification. Patients should be made aware of this when initial therapy is being discussed" and to "Be aware that initial drug treatment with repaglinide should be stopped and the drugs in the dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug." This information is also reflected in the algorithm.
586	Oxfordshire CCG	Full	198	General	There is a concern that despite repaglinide showing to be consistently associated with the largest reduction in HbA1c at 3, 6 and 12 months, it has a greater number of hypoglycaemic events. This would affect the quality of life of a newly diagnosed patient.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
58	Oxfordshir	Full	199	Gen	The use of pioglitazone was also a cause of	Thank you for your feedback. The guideline

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7	e CCG			eral	concern. It is not recommended for people with heart failure or a risk of osteoporosis and that this may reflect a large proportion of target patient population making it an inappropriate treatment step. This is not taking into account the MHRA warning regarding heart failure and bladder cancer for this drug	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. In addition, a footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
582	Oxfordshire CCG	NICE	20	47 -49	We agree that metformin should be first choice and that the dose should be gradually increased.	Thank you for your feedback.
583	Oxfordshire CCG	NICE	20	50	To consider repaglinide as initial treatment if metformin is contraindicated or not tolerated would be very challenging. This is because it would be a major change in a treatment pathway and it is known that our local secondary care colleagues have concerns and have responded. It would place GPs in a difficult position as there may be differences to the recommended treatment pathway and that which may be coming out of secondary care.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors,

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						pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, a generic recommendation has also been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
592	Oxfordshire CCG	Full	256	20	The statement that sodium glucose transporter 2 may be appropriate for some people but are beyond the scope of this guideline despite mentioning NICE TA288 and TA315 is unhelpful. The guidance should be comprehensive and detail which patients would be appropriate for SGLT2 therapy.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
593	Oxfordshire CCG	Full	260	17	This states that the meglitinides do not have adequate longitudinal studies to understand long term safety issues. Therefore this is at odds with your recommendation	Thank you for your feedback.
907	Primary Care Diabetes Society	Full		50	If standard release Metformin is not tolerated, the use of modified release metformin should be considered (as per type 1 amended guideline p341). Although there is little evidence addressing the benefit of modified-release, it is	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the

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					assumed that its benefits and efficacy are similar to standard Metformin but with better tolerability, From our survey of members, 84% were happy to use metformin as a first line therapy and 95% would wish to change to modified-release preparation before changing to an alternative drug class. (A survey of PCDS members regarding the draft NICE Type 2 guideline was undertaken during January/February 2015 and the results of this have helped inform this response).	appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
909	Primary Care Diabetes Society	Full		51	Pioglitazone is suggested as the most appropriate second line therapy before consideration of other agents. In our survey, over half of clinicians (57%) were unhappy to use Pioglitazone, citing concerns over cardiac safety, weight gain, fluid retention, fracture risk and cancer concerns. The PCDS feel that there should be an equal weighting of Pioglitazone, DPP4 inhibitors, Sulphonylurea therapies and Sodium Glucose Reuptake 2 inhibitors, with an emphasis on individualisation of care around the patient. This should take into account the patients' expectations, perceived targets and co-morbidities.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
910	Primary Care	Full		52	We acknowledge that sulphonylurea therapies are an important part of the diabetes formulary,	Thank you for your feedback. The guideline development group has reflected on the clinical

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	Diabetes Society				but suggest that there are cautionary notes regarding risks of weight gain, hypoglycaemia and cardiovascular safety. There should also be emphasis that patients should be advised that they may need blood glucose monitoring.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
903	Primary Care Diabetes Society	Full	16	2 Line 10	1.5 recommendation : There should be a comment to suggest a review and reinforcement of knowledge/education at each escalation in therapies	Thank you for your feedback. This recommendation has not been updated therefore it is not possible to many changes.
904	Primary Care Diabetes Society	Full	19	.38	Set an ***INDIVIDUALISED*** HbA1c target. For most individuals this will be HbA1c 48mmol/mol	Thank you for your feedback. Recommendation 1.6.5 provides generic guidance on ensuring that patients are involved in setting individual targets.
905	Primary Care Diabetes Society	Full	20	44	Blood glucose monitoring to be considered when using as part of a structured education to help engage patient with the management of their conditions	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. NICE anticipates that diabetes education and curriculums for healthcare professionals will change and continue to develop based on the latest review of the best available evidence.
90	Primary	Full	20	47	Metformin should be titrated up to a dose of 2g	Thank you for your feedback. As per NICE

Type 2 diabetes (update)

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6	Care Diabetes Society				daily or maximum tolerated as per side effects and renal threshold.	guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.
908	Primary Care Diabetes Society	Full	20	50	Repaglinide we consider as a poor alternative to Metformin as a first line agent. 70% of our members surveyed would be unhappy to use this agent. The main concern was with its multiple times/day dosing, its inability to use with other agents, together with concerns of hypoglycaemia, weight gain and lack of familiarity with its use. We also note that it is considered as an alternative to Metformin but not as a second line agent. Repaglinide's dosing regimen and inability to use with other agents may lead to significant prescribing errors and risk of patient harm. Repaglinide is a prandial glucose regulator, and as such, it will not be able to maintain HbA1c. In order to escalate therapies, repaglinide would need to be stopped and an alternative agent substituted in its place - Pioglitazone takes 6-8 weeks before it achieves a reasonable glucose-lowering action. This would mean that the patient's diabetes will deteriorate prior to any therapeutic increase. - Sulphonylureas at the equivalent maximum dose of repaglinide are likely to place the patient at significant risk of hypoglycaemia	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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					- DPP4 inhibitors would be the only safe option to substitute at this level, therefore limiting the choices that clinicians would have for individualising care.	
911	Primary Care Diabetes Society	Full	21	54	The use of Repaglinide only as an alternative to metformin and the inability to use it with any other diabetes therapy is likely to cause confusion and place patients at risk .Before escalating therapies, Repaglinide would have to be replaced by an alternative agent. As stated previously, this will place patients at risk of delay in treatment.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has ALSO given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
912	Primary Care Diabetes Society	Full	21	55	There should be advice that the combination of Pioglitazone and a sulphonylurea can lead to weight gain	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs,

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						available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
912.5	Primary Care Diabetes Society	Full	22	61	The stopping criteria for the use of GLP1 analogues should be reviewed. In clinical practice, we are aware that some patients may make significant improvements in weight or glycaemia but not necessarily in the two parameters. We would suggest that achieving the weight loss OR the HbA1c target should allow the clinician to continue prescribing these agents. In our survey, change in the stop criteria to allow ongoing prescribing if one of the targets was achieved, was supported by 91% of our members.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
913	Primary Care Diabetes Society	Full	24	68	No mention has been made of using Pioglitazone or an SGLT2 inhibitor as an insulin sparing agent.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
914	Primary Care Diabetes Society	Full	General	General	**NICE guidelines** The NICE guidelines have, to date, been generally well received and respected by the	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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					health care community both nationally and abroad. NICE guidelines offer the health care professional cost effective, evidence based direction for clinical practice. It is therefore regrettable that in regard to the current draft guideline on Type 2 diabetes, these notable characteristics of a respected guideline must be called into question. The PCDS is unable to support the new guidelines as they stand as they appear to be based solely on drug acquisition costs rather than a reflection of cost effective and safe practice. **<u>Metformin</u>** Its use as a first line agent has been established with cardiovascular data, effectiveness and long term management of target attainment. We accept that this should remain the first choice following lifestyle management. It is estimated that 10-15% of the population are unable to tolerate Metformin due to gastro-intestinal side effects. Rather than suggesting a trial of Metformin modified-release, NICE has suggested that an alternative agent should be used. Metformin has been proven to have significant cardiovascular outcome data and remains weight neutral. Accepting that there is limited data on Metformin as a modified release preparation, it is still felt that it should be considered for those patients who are unable to tolerate metformin normal release before	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the

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					moving on to an alternative therapeutic group. (1, 2, 3, 4, 5) There is no advice in the guidelines as to how high and at what rate dose titration should be managed. Most studies have shown that 2g daily appears optimum level between achieving control and tolerability We are pleased to see that NICE accepts the use of Metformin down to an eGFR of 30 with caution. **Repaglinide** - Repaglinide has been proposed as an alternative initial therapy in patients who are unable to tolerate Metformin. This is a drug that will be unfamiliar to many clinicians and we must advise caution in its use. - Repaglinide is a fast acting secretagogue. This would suggest that it can be used to induce insulin production only at meal times and thereby treat prandial hyperglycaemia. It is suggested that this will reduce the risk of hypoglycaemia and weight gain associated with sulphonylurea therapies. Unfortunately data suggest there remains a significant risk of these complications. (6) - We advise against the consideration of Repaglinide due to :-- Significant risk of weight gain and hypoglycaemia that in the long term would negate acquisition cost savings by the	changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. Based on the updated evidence review and health economic analysis, the guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Recommendation 1.6.27 (NICE version) includes

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					increased need for medical intervention, hospitalisation and development of morbidities associated with weight gain. Multiple daily dosing. Repaglinide requires pre-meal dosing that is likely to result in issues regarding adherence to the therapy regimen. Multiple levels of dose increments. Often patients may require different doses at different meals, depending on the carbohydrate load of their food. This can result in confusion and complicated regimens. (7, 8) Increased frequency in blood glucose monitoring to ensure correct meal time dose of therapy and to prevent risk of hypoglycaemia. The short duration of Repaglinide means that it is a useful prandial glucose regulator but will be unable to influence fasting glucose levels. Therefore, its ability to help patients achieve their target HbA1c is unlikely without additional agents. NICE have suggested that it should only be used as a monotherapy and surprisingly have not considered it as an add-on to metformin. NICE has not commented on dose titration and at what level alternative agents should be considered. At the level when Repaglinide is seen as not sufficient for control of glucose levels, this	people with a BMI less than 35kg/m^2 and the following caveat to adjust BMI accordingly for people from black, Asian and other minority ethnic groups. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

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					agent will have to be discontinued before the addition of any other agent due to its licence. This will place patients at an increased risk in the transition phase. There is limited long-term outcome and cardiovascular safety data on repaglinide. - The PCDS feel that the use of Repaglinide is a significant concern in the Draft NICE Guidelines and will cause confusion in the management of patients, failure to adequately achieve targets and place patients at risk from poor compliance, hypoglycaemia, weight gain and the difficulty that clinicians will experience in intensification of therapy. **<u>Pioglitazone</u>** Following the recent concerns regarding Pioglitazone, The PCDS are surprised that it features so prominently in the Draft Guidelines. Pioglitazone is a useful therapy in a limited number of people with diabetes. It has proven that it is effective over the long term for controlling HbA1c (ADOPT Study), but due to side effects of this therapy, its use has significantly reduced and has become limited to only certain patient phenotypes. Pioglitazone carries a significant co-morbidity of	

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					weight gain and fluid retention (9, 10). As a large numbers of patients with Type 2 diabetes are overweight, have cardiovascular disease and are likely to be on cardiac, anti-hypertensive therapies that will lead to oedema, many Primary Care clinicians will therefore avoid prescribing this therapy. Pioglitazone has also been associated with increased fracture risk, macular degeneration deterioration and linked with bladder cancer. Although the latter association is now disputed, there remains caution in its prescribing. Furthermore any association between Pioglitazone and bladder cancer is strengthened by length of use and cumulative dose, raising further questions over its early adoptive use in a National Guideline. Due to the predominance of middle age, elderly and female populations, the concern of fracture risk is high as well as possible deterioration in vision for other reasons than diabetes. The draft guidance implies that Pioglitazone should be the second choice to Metformin treatment. The PCDS are concerned that this may increase the use of Pioglitazone in patients who may not be totally suitable. We agree that it should be suggested that it can be considered,	

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					but not emphasised as the primary second choice in intensification. **<u>Sulphonylurea</u>** By the fact that these therapies are no longer suitable to be considered as an alternative to Metformin, it must be assumed that NICE have accepted the general medical opinion that these therapies carry a significant risk of weight gain and hypoglycaemia (11). We are therefore concerned that they remain as an alternative as a second line agent when NICE appears to have concluded that short-acting secretagogues are safer. Their place in the guideline is confusing and suggests that this is due to cost and prescribing licence rather than patient safety. We would suggest appropriate emphasis is placed upon when the drugs should be considered, taking into account their risks. **<u>Dipeptidyl Peptidase 4 Inhibitors</u>** The PCDS agree that these therapies should be considered as a second intensification step. We would also suggest that they may have a role as a first line therapy in patients who are unable to take Metformin and have significant concerns regarding hypoglycaemia. Recent publications have also suggested they may be useful	

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					therapies in people with cardiovascular disease. The PCDS feel that the most cost effective DPP-4 inhibitor should be used rather than solely considering the cheapest acquisition cost, and emphasis made regarding renal monitoring and dose adjustment depending on the DPP-4 inhibitor chosen. **<u>Sodium –Glucose Transport Inhibitors</u>** These have become a useful therapeutic agent in the management of overweight and obese people with type 2 diabetes. It is appreciated that they remain outside the scope of the draft documentation but as they are likely to become more prominent in diabetes management, the PCDS strongly recommend inclusion of their appropriate use in the guidelines. Due to the benefits of blood pressure and weight improvement, their place should be before Pioglitazone. *(With perhaps consideration of criteria to start and stop therapy)* **<u>GLP-1 analogues</u>** GLP-1 analogue therapies have been useful in managing both weight and glycaemic control. Concerns remain with their high costs and newer agents are entering the market. The	

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					GLP-1 analogues have differing characteristics that should result in individualised choice of preparation and device. The draft guidelines offer no advice regarding daily or weekly dosing. We assume this is because costs are similar. The NICE Draft guidelines has kept the criteria for starting and stopping GLP-1 analogues the same as previous technology appraisals/NICE guidelines. We agree that there is a rationale for the starting criteria but would rather it include the obese group as well as the morbidly obese. .We would also recommend much lower BMI specified cut-points for black and ethnic minorities groups as per the NICE Guidance PH46. We feel that the stopping criteria should be reviewed. Many patients can achieve a reduction in both HbA1c and weight, however some only achieve target in one parameter. We would argue that stopping therapy when the target has been achieved in weight or HbA1c is inappropriate and not based on any clinical evidence. The next alternative is to switch to insulin which will lead to further weight gain and co-morbidities. There is now good evidence to support the use of GLP-1 analogues with insulin therapy. NICE suggest that this should only be used under diabetic specialist care. Primary Care has been involved in both GLP-1 analogue initiation as	

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					well insulin management for many years. If the individual practitioner's skill level includes the ability to manage such therapies, we feel the combined use should not be barred from Primary Care. **Insulin** NPH insulin has remained the first choice of insulin within the draft guidelines. NICE have advised that analogue insulin may be used in appropriate patients subject to hypoglycaemia or where twice daily dosing is needed. We would like to emphasise that when converting between insulin types, advice must be given that doses may not be the same and regular blood glucose monitoring should be encouraged. **Safety and prescribing in fertile females** We feel that this is an important foot note for this document, even though it is covered in the NICE pregnancy guideline published in February 2015. Due to the increased prevalence of Type 2 diabetes at a younger age, there is concern that women may become pregnant on therapies that are not licensed or safe for use during pregnancy. A list of therapies to avoid or use with caution in this group of patients would add to the clarity and safety of the guideline.	

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					As the leading representative organisation for the management of Diabetes in Primary care, we are unable to support this draft guideline as it stands. We appreciate the time and effort that has gone into this guideline and are fully aware that significant changes will have both a time and a monetary cost but we feel that the draft guidance cannot be safely used in clinical practice. It is not evidence based, is subject to misinterpretation and lacks clarity, leading to both confusion in patient care and risk of patient harm. The PCDS ask that the draft be reviewed and our concerns that we have expressed be duly noted. We propose that delaying the publication of the final guideline to ensure that this is a document that can be used and respected is far more important than publishing a guideline that will harm the reputation of NICE and possibly result in harm to people with diabetes. We believe that this guidance has been strongly influenced by drug acquisition costs rather than being based on the broader medico-economic evidence currently available for diabetes management. 1.Fujioka K et al ClinTher 2003;25(2):515-529, 2. Fujioka et al Diabetes Obesity and Metabolism 2005:7:28-39, 3.Donnelly L.et al Diabetes Obesity and	

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					Metabolism 2009 :11:338-342, 4.Blonde L et al Curr Med Res Opin 2004; 20(4):565-572, 5. Feher et al Br J Diab Vasc Dis 2007: 7 (5):225-228). 6. Phung OJ et al The effect of non-insulin anti diabetic drugs added to metformin therapy on glycaemic control, weight gain and hypoglycaemia. JAMA 2010; 303;1410-18 7. WHO Adherence to long term therapies. Evidence for action Switzerland 2003 8. Grant R W et al Polypharmacy and medication adherence in patients with Type 2 diabetes. Diabetes Care 2003;26:1408-12 9. Dormandy J A et al PROactive investigators. Lancet 2005;366:1279-1289 10.Colbourn H M et al. Scottish Diabetes Research Network epidemiology group. Diabetologia 2012 ; 55:2929-2937 11. UK Hypoglycaemia Study Group Diabetologia 2007;50:1140-1147 <u>The PCDS are the premier voice for clinicians who deal with diabetes in Primary Care. To help our members understand the draft guideline, we ask NICE to address some important questions.</u> 1) Whilst we agree that there is sparse prospective RCT data on the tolerability of Metformin MR there is retrospective cohort data and pragmatic	

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					uncontrolled data pointing to better tolerance of the modified release preparation PARTICULARLY IN THOSE PATIENTS SWITCHED FROM IMMEDIATE RELEASE TO MODIFIED RELEASE. With this in mind, coupled with the prescribing experience both of the PCDS Committee and of our survey sample, (both of whom favour and regularly prescribe the MR version in plain metformin intolerant patients) could the Guideline Development Group (GDG) please explain why this option is currently not recommended in the Draft Guideline? 2) Given that the only sizeable head to head study of Repaglinide versus SU (Derosa et al) shows no advantage both in terms of glycaemic control and hypoglycaemia, would the GDG please explain the advantages of the former, considering that its multiple daily dosing and incremental dosing requirements will have a significant effect on adherence to the regimen. 3) Are the committee not aware that there will be confusion and risk of significant deterioration in glycaemic control when intensifying therapy following Repaglinide and if so how is the impact of this to be minimised? 4) Following the information provided by the survey of our members, are the GDG concerned that the guideline will not be followed and thereby have a detrimental effect on the	

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					standing of NICE as an organisation?	
823	Roche Diabetes Care Limited	Full	12	8-13	Please also consider unstable metabolic states as a reason for offering self-monitoring of blood glucose levels for adults with type 2 diabetes, eg. • Within newly diagnosed patients • Change in therapy / lifestyle, dosage adjustment • Intercurrent illness The use of self-monitoring of blood glucose (SMBG) as educational tool are other reasons to offer SMBG.	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring of blood glucose (SMBG) in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. There was no evidence to indicate that SMBG in newly diagnosed patients or in individuals undergoing changes in therapy/lifestyle/dose adjustment was clinically or cost effective. The guideline development group has made a research recommendation on the effectiveness of short-term SMBG for acute intercurrent illnesses.
827	Roche Diabetes Care Limited	Full	141	11-15	It is the position of Roche Diabetes Care that SMBG can, in fact, facilitate long-term improvement in glycaemic status, but only when the following conditions are met: • The SMBG regimen is structured (both in timing and frequency) to obtain actionable information about each patient's glucose control. • The data are generated and documented in a manner that facilitates analysis and discussion of glycaemic patterns between patient and healthcare provider. • Both the patient and healthcare provider	Thank you for your feedback. The 4 criteria that you outlined for self-monitoring of blood glucose levels (SMBG) to facilitate long-term improvements should be implementable in routine clinical practice. Individuals volunteering to participate in clinical trials are typically considered to be more proactive and compliant than the average clinical population. The individual quality of the 17 included trials for the comparison SMBG and no SMBG in the review ranged from low to high. Notwithstanding, all analyses indicated that SMBG compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c. Moreover, none of

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					are well-educated, willing and skilled to make appropriate treatment decisions based upon the SMBG data. • Both the patient and healthcare provider mutually agree upon treatment decisions and modifications. Unfortunately, these criteria for appropriate SMBG use are absent from the interventions used in many of the studies (eg. DiGEM, ESMON, Davidson) analysed in the guideline. For example, in the DiGEM trial, changes in pharmacologic therapy were based primarily on HbA1c levels. Although information about clinician review or utilisation of SMBG results was not included in the study report, it would be reasonable to assume that analysis of patient glucose data by clinicians occurred infrequently, if at all. Various studies demonstrate a high degree of variability and heterogeneity to which the criteria for appropriate SMBG use were applied. Furthermore, "most trials did not give any details on changes made to therapy or life style based on SMBG" and no trials reported patients being actively encouraged to make behaviour/lifestyle changes based on results of SMBG. No feedback on results was given to patients. There appears to be a difference in expectation between HCPs and patients, in that patients expect HCPs to decide based on the readings they provide, whereas HCPs see SMBG as a	the subgroup analyses based on existing treatment (that is diet alone or combined with oral antidiabetic and/or insulin medicines), type of SMBG (standard or enhanced) or overall prescribed frequency of SMBG testing (that is less than once a day, 1 to 2 times a day or more than twice a day) showed a clinically important reduction in HbA1c levels.

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					tool for patients to make behaviour/ lifestyle changes. SMBG readings were taken at inappropriate times and so it was impossible to gain meaningful results. " (Clar, Barnard et al. 2010) "… SMBG is best used to motivate adherence to dietary recommendations and self-management behaviours. If the patient is not taught empirically based strategies to improve glucose levels, the effects of SMBG on HbA1c will be minimal. SMBG leads to an increased adherence to dietary recommendations and education on diet. SMBG indirectly led to improved HbA1c by increasing weight loss."(McAndrew, Napolitano et al. 2012) Finally, Jansen showed adjusted for baseline HbA1c in a meta-analysis a 0.42% HbA1c reduction of SMBG vs. no self-monitoring and of 1.13% HbA1c reduction for enhanced SMBG vs. no self-monitoring (Jansen 2006). Roche Diabetes Care is concerned that this can create some significant limitations regarding the conclusions drawn from the pooled and averaged data. The inclusion of trials in which subjects had relatively low baseline HbA1c values somewhat skews the findings. For example, subjects in all arms of the DiGEM trial (Farmer, Wade et al. 2009) had mean baseline HbA1c values ranging from 7.41% to 7.53%. At the time this trial was conducted, <7.5% HbA1c was considered acceptable glycaemic control	

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					according to UK diabetes treatment guidelines (NHS National Institute for Health and Clinical Excellence (UK 2008). This would certainly explain why treatment intensification was so minimal; use of oral diabetic agents was increased in only one third of DiGEM patients (Farmer, Wade et al. 2009). As a result, little improvement in HbA1c was seen at study end. "The DiGEM trial has been criticised on similar grounds because control was quite good at baseline (mean HbA1c level = 7.5%), making further improvements difficult.98" (Clar, Barnard et al. 2010) Roche Diabetes Care strongly supports all research that expands our understanding of diabetes management and leads to improvements in patient care, especially when used for decision making of patients and physicians. Rather than focusing time and resources on trying to determine whether performance of SMBG impacts glycaemia, we should ask the more relevant question: Does appropriate use of SMBG data improve clinical outcomes? Recent evidence like the STeP study strongly suggests that it does.	
829	Roche Diabetes Care Limited	Full	151	12-13	Regarding "The Canadian HTA (Cameron et al. 2010) had few 12 limitations...", please consider the following: "The COMPUS analysis provides an illustration of how modelling assumptions can lead to very conservative estimates of long-term cost	Thank you for your feedback and detailed appraisal of the COMPUS analysis. Your concerns with their randomised controlled trial (RCT) quality assessments, study design issues, impact of adherence and frequency of testing, unit costs, UKPDS outcomes model generic

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					effectiveness for SMBG": **Clinical Effect** As with all treatments or management tools for diabetes, evidence for the clinical benefit of SMBG is dependent upon attributes of source studies. These include protocol design and implementation, actual SMBG use (ie. adherence level), concurrent treatment regimen and data analytic approach. Important for this discussion is that the SMBG HbA1c advantage of -0.25% assumed for the COMPUS base case can be considered conservative. This value is similar to effects reported in meta-analyses that emphasized findings by Farmer et al.,[27] or other studies in which SMBG results were not used to adjust diabetes management regimens.[44,45] However, it is lower than the range of HbA1c advantages (-0.39% to -1.23%) found in several other meta-analyses.[46-48] Using the SIGN Checklist 2, four RCTs[35,36,37,39] were classified by COMPUS as being of 'poor' quality and three[27,34,38] of 'good' quality.[40] This checklist is one of several instruments available to assist in RCT quality assessments. However, it contains some items relevant to studies in which 'blinding' is critical, and that have minimal applicability to SMBG trials not optimally conducted with single- or double-blind	concerns and assumed treatment effect size for health economic modelling were noted. The quality assessment existing health economic studies is defined by the NICE guidelines manual (2012) and focusses on modelling aspects rather than a full quality assessment of the underlying clinical evidence. The COMPUS work was viewed to have few limitations in respect to this checklist (full details are given in table 40 of the full guideline). The guideline development group considered this evidence alongside a number of other existing economic stuides. As recorded in the Linking Evidence to Recommendations table (see section 8.3.3 in the full guideline), in assessing the quality of the evidence, the guideline development group placed particular emphasis on the country costs used and the source of the HbA1c change estimates. In this context, they gave greatest weight to the UK cost and RCT based analyses and least weight to non-UK studies based on observational American data. They also noted the high degree of uncertainty displayed by the cost utility analyses (CUAs) and felt that, whilst it was not possible to state conclusively that SMBG is or is not likely to be cost effective compared to no self-monitoring, the most applicable evidence with least limitations suggested that self-monitoring is not likely to be cost effective

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					protocols.[40] Appropriately, ratings of 'high' quality also depend on low withdrawal rates, and an intent-to-treat (ITT) data analysis. Unfortunately, ITT analyses (which consider only original group assignments) do not address the challenge of capturing clinical benefits when monitoring adherence levels among remaining study participants are low.[49] Footnote 2: A meta-analysis by Poolsup et al.,[49] using a standardized scale, rated three RCTs[35,36,39] as having 'good' quality based on reporting of adherence levels. These three had received a 'poor' quality rating in the COMPUSreview.[40] Noteworthy in the COMPUS assignment of weights is that the study by Farmer et al.[27] (showing the smallest HbA1c advantages for SMBG of the seven RCTs) received two separate ratings of 'good'. This three-arm trial had compared both (i) a 'more intensive education' SMBG group (n = 151) and (ii) a 'less intensive education' SMBG group (n = 150) to the same 'no SMBG' or 'usual care' control group (n = 152). Among RCTs included in the COMPUS review, HbA1c advantages (SMBG over no SMBG) at endpoint ranged from -0.155%[27] to -0.70%.[37] Three trials reported differences of -0.20% to -0.28%,[34-36] while two showed larger advantages (-0.40%[38] and -0.46%[39]).	compared to no self-monitoring.

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					Clinical (HbA1c) benefits associated with SMBG tend to be larger when derived from observational or retrospective studies [17,18,50] rather than from RCTs. As COMPUS researchers correctly noted, non-randomized studies are subject to a variety of potential confounds.[30,40] However, there are also many non-trivial limitations when the magnitude of SMBG effect is derived from RCTs.[12,51-54] For example, in at least four of the included RCTs,[27,34,35,38] patients were precluded from obtaining timely feedback on SMBG results, and thus potentially modifying their behaviour and/or discussing treatment alterations with healthcare providers. It was one of the key limitations of the Farmer et al.[27] study,[51,52,55] and contributed to the decision by the UK National Institute for Health and Clinical Excellence (NICE) to discount the trial in a recent update to its guidance document on type 2 diabetes management.[56] Adding to the challenge of estimating SMBG effects was the range of SMBG frequency required by RCT protocols, and the actual level of monitoring that could be discerned.[15,31] Overall, there was a paucity of information on the numbers of patients who continued to monitor, and at what frequency. When data were reported, the average level of monitoring was, in almost all instances, below protocol	

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					requirements. Table II in the SDC provides a summary of monitoring requirements for the seven RCTs, as described in their respective publications and as expressed in the more standard 'per day' metric for SMBG. Also included are actual SMBG frequencies (if reported), and the applicable category (<1 per day, 1–2 per day, >2 per day) assigned by COMPUS for sub-analyses.[7] Finally, the table shows HbA1c effects and daily use assumed for each of the three categories. Non-adherence with recommended levels of SMBG can present both clinical and empirical challenges.[57] The study by Farmer et al.[27] provides an illustration of how <100% adherence can contribute to the underestimation of SMBG effect. Despite a low withdrawal rate, there were relatively low levels of monitoring, even for patients who 'remained' in their randomized group.[27] Only 67% of patients assigned to the SMBG 'less intensive education' group continued to monitor at least twice a week for the 12-month period. Because only 52% of those assigned to the 'more intensive education' SMBG group continued to monitor at even these minimal levels, almost half of HbA1c data attributed to the SMBG 'more intensive' group at endpoint were provided by patients who had not been monitoring for a substantial length of time.	

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					Patient Characteristics Simulated cohort characteristics are defined by demographics, and by clinical risk factors assigned at 'baseline' (i.e. start of the clinical trial). For the UKPDS model, demographic parameters include age, ethnicity, sex, diabetes duration, weight and height. Risk factors include HbA1c, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) and smoking history/status.[58] Complication history is represented by presence or absence of atrial fibrillation and/or peripheral vascular disease (PVD) at diagnosis, as well as by years since each of the seven diabetes-related events. COMPUS base-case cohort assumptions can also be considered conservative (refer again to table I in the Supplemental Digital Content). Although the average HbA1c (8.4%) was above the clinically recommended value of 7.0%,[19,20] and the mean duration of diabetes >4 years, patients were assumed to have no history of diabetes- related complications.3 It could be argued that this type 2 diabetes cohort would be expected to have a history of at least the less-severe complications (e.g. atrial fibrillation) that are precursors to the more	

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					serious events (e.g. stroke) modelled.[5] A spuriously 'healthy' cohort would benefit less from SMBG than would a more representative Canadian population of type 2 diabetes patients primarily on OADs.4 There would be lower risks of developing the longer-term complications that, if reduced, could provide economic and quality-of-life benefits to offset strip acquisition costs. Although assuming a more representative complication history at baseline has the advantages previously described, a key feature of the UKPDS model presents a related challenge in capturing potential SMBG-associated reductions in complications. Because the model simulates only first events[33,58] and recurrent events are not captured, the HbA1c-lowering benefits (ie. decreased risk of both first and subsequent complications) are underestimated. The incidence of complications can be substantially underestimated for an older patient cohort and/or those with a history of diabetes-related complications. It should be noted that COMPUS researchers did conduct a sensitivity analysis to incorporate more representative baseline complication rates.[6,7] The multi-way (simultaneous modification of >1 variable) analysis assumed an SMBG frequency of <1 per day and an HbA1c advantage of -0.26%. Although the ICER decreased to	

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					approximately $Can90 000 per QALY gained,[7,30] a greater reduction could have been expected if the analysis had not also included a 10% increase in strip costs and a modification in baseline HbA1c (from 8.4% to 7.5%). **Cost Assignments** **Complication Cost and SMBG Strip Acquisition** The extent to which acquisition costs of a treatment or a management tool such as SMBG may be offset by savings associated with fewer complications is influenced by a priori unit cost assignments.[59] In the COMPUS base case, costs ($Can, year 2008 values) assigned for non-fatal events (at time of event) were as follows: IHD ($Can5394); MI ($Can17 324); heart failure ($Can15 766); stroke ($Can23 475); amputation ($Can36 416); blindness ($Can2884); renal failure ($Can23 365).[7] 6 A 2003 publication by O'Brien et al.[5] illustrated the conservative nature of these assignments. Canadian-specific cost data for type 2 diabetes complications were obtained from several sources, with provincial values adjusted to calculate 'national' costs. Event costs for an acute MI and a stroke were $Can18 635 and $Can33 256, respectively, and the state cost for renal failure was $Can63 045. These $Can, year 2000, unit values are larger than those assigned	

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					by COMPUS to represent their year 2008 costs. Just as poor adherence to SMBG can lead to an underestimation of clinical effect, it can also result in an over-estimation of strip usage and therefore, acquisition costs. In a COMPUS sub-analysis of three SMBG frequency categories (<1 per day, 1–2 per day, and >2 per day), strip costs were based on assumed averages of 0.77 per day, 1.46 per day, and 3.5 per day, respectively (refer again to table II in the SDC). For the latter two categories, current calculations of average frequency in the RCTs were lower: 1.29 per day and 3.14 per day. When viewed from a daily cost perspective, small differences in assumed average frequency may appear inconsequential. However, when SMBG costs are simulated over 40 years, their impact on cost-effectiveness results is potentially substantial. **Pathway of Clinical Effects and Complications** Specific aspects of the UKPDS model render it less than optimal for estimating comparative costs and effectiveness, particularly in patients whose type 2 diabetes is not newly diagnosed.[58] The structure limiting complications to first events, and its impact on potential long-term cost offsets has been addressed. The COMPUS report stated that the modelled estimate of HbA1c SMBG effect was	

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					assumed to follow trajectories from published UKPDS equations and algorithms.[7] Not explicit was that if no updated risk values (e.g. HbA1c advantages subsequent to year 1) are supplied as inputs, UKPDS model default paths result in the two (SMBG and control) HbA1c curves converging by approximately years 7–8.[33] Assuming convergence relatively early in a 40-year simulation markedly reduces the ability to demonstrate potential long-term benefits of a treatment or management tool such as SMBG.[32] In modelling the cost effectiveness of conventional versus intensive glucose control in newly diagnosed type 2 diabetes, UKPDS investigators considered the model that allowed observed treatment effects to continue beyond the trial period to have produced a more unbiased estimate than did the more conservative model that forced treatment effects to zero at clinical study closure.[60] A final point regarding the simulation pathway concerns clinical risk factors other than HbA1c. The COMPUS analysis specified no changes in total cholesterol, HDL-C or SBP beyond those of UKPDS default equations. A modelling study by McEwan et al.[61] provided evidence for the importance of assessing changes in cholesterolelated risk in type 2 diabetes. Over 20 years, costs were impacted most significantly by changes in HbA1c and the ratio of total	

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					cholesterol to HDL-C. Additionally, the role of sustained blood pressure control in reducing type 2 diabetes complications was recently corroborated by results of a UKPDS post-trial monitoring study.[62] The incorporation of changes in these clinical parameters would help to more accurately assess benefits that could favourably impact longer-term complications such as coronary heart disease, the leading cause of death in patients with diabetes.[5] **Summary** A variety of conservative inputs of the COMPUS SMBG cost-effectiveness analysis, and limitations of the UKPDS model were reviewed. The HbA1c advantage associated with SMBG (-0.25%) was influenced by RCT protocol heterogeneity and limitations (e.g. low adherence), and by weighting procedures. The base-case patient cohort was at relatively low risk for developing serious and costly diabetes complications. Moreover, the possible economic benefits of avoided events were minimized through relatively low values in unit costs assigned to individual complications. A particularly important assumption was that the time paths for both SMBG and 'no-SMBG' cohorts would follow UKPDS default equations, with HbA1c values converging relatively early in the 40-year simulation. Table III in the SDC provides a summary of	

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					many conservative assumptions, and a list of relevant sensitivity analyses conducted by COMPUS. The following sections are intended to build upon the review, and illustrate how a minimal number of key alternative assumptions can lead to different results (reduced ICERs) and conclusions regarding the cost effectiveness of SMBG in Canada.7" (Tunis 2011)	
828	Roche Diabetes Care Limited	Full	160	25 - 32	1) Scherbaum et al.: The baseline HbA1c values are between 7.2 and 7.5%: The authors emphasize that these results only apply to patients with stable metabolic control and without any necessity of changing anti-diabetic medication: a) one vs four tests a week b) before study start (not re-educated) in both groups: structured education on diabetes mellitus, SMBG instructions c) no explanation given for higher HbA1c after 12 months in high SMBG group d) confidence intervals do overlap and the point estimates for intervention and control arm are covered by the confidence interval of the respective trial arm and p-values are above 0.5: low: 6.9+-1.0; high: 7.1+-1.0: Consequently, there is no significant difference between the comparison arms (Scherbaum 2008).	Thank you for your feedback. A study by Scherbaum that matches the stated characteristics has been included in the evidence review (see section 8.3.2.2 in the full guideline). A paper by Johnson 2006 has been excluded from the clinical evidence review because it did not meet the inclusion criteria as it focused on availability/cost of self-monitoring of blood glucose (see Appendix L Excluded list of studies).

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					2) Johnson et al.: baseline HbA1c: Intervention 7.5; Control 7.3 a) intervention: free test strips b) the intervention group tested effectively one day more than control based on complete data c) both groups showed a -0.2 reduction in HbA_{1c} after six months d) pharmacists recommended • 7 tests per week when on OAD 3-4 times • on diet in both groups: once daily, 3-4 times per week (Johnson 2006) The two studies are based on baseline values of HbA1c between 7.2-7.5%. As in the DiGEM trail, little improvement in HbA1c was seen at study end. Besides that the trial by Johnson et al. focuses on the economic parameter of free access to strips rather on making enhanced SMBG a success. The meta-analysis is based on the one hand on a non-significant difference and on the other hand on an equal HbA1c reduction starting from different baseline values.	
824	Roche Diabetes Care Limited	Full	19	3-5	Without routinely performed SMBG, it may become difficult to investigate unexplained discrepancies between HbA1c and other glucose measurements.	Thank you for your feedback. This generic recommendation is relevant to individuals who have had other glucose measurements. This does not necessarily need to have been via self-monitoring of blood glucose.
825	Roche Diabetes	Full	27	37-3	Concerning non-insulin-dependent diabetes, the STeP study (Polonsky, Fisher et al. 2011) has	Thank you for your feedback. The STeP trial (Polonsky 2011) and Franciosi (2011) study have

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	Care Limited		-28		shown that using the structured testing approach "ITT analyses showed that the mean (SD) number of daily blood glucose tests, even when including the 7-point Accu-Chek 360° View blood glucose analysis system profiles for the STG[2], was significantly lower for the STG than for the ACG[3] at month 6 (0.97 [0.81] vs. 1.21 [1.00], P = 0.007); month 9 (0.85 [0.72] vs. 1.11 [0.84], P = 0.001); and month 12 (0.77 [0.69] vs. 1.05 [0.80], P < 0.0001)." The STeP study was a large prospective, cluster-randomised, multi-centre trial evaluating the use of structured SMBG in 483 poorly controlled (HbA1c ≥7.5%, insulin-naïve T2DM patients from 34 US primary care practices (Polonsky 2011). The primary endpoint was change in HbA1c over time. Patients in the structured testing group used a simple paper tool that facilitates collection and interpretation of 7-point glucose profiles over 3 consecutive days. These patients completed the tool on a quarterly basis, brought the completed tools to medical visits and discussed findings with their physicians. Structured testing group patients received	been included in the evidence review for the guideline (see section 8.3.2.2).

[2] Structured testing group

[3] Active control group

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					training in blood glucose measurement, including instructions for how to identify problematic glycaemic patterns and how best to address such problems through changes in physical activity, portion sizes, and/or meal composition; structured testing group physicians received an algorithm describing various pharmacologic/lifestyle treatment strategies that could be used in response to the specific SMBG patterns identified. Active control group patients received enhanced usual care only and were instructed to use their meter following their physicians' recommendations but received no additional SMBG prompting, training, or instruction. At 12 months, intent-to-treat (ITT) analysis revealed that structured testing group patients (n=256) experienced significantly greater improvement in mean HbA1c than active control group patients (n=227): -1.2% vs. -0.9%; P=0.04. Per protocol (PP) analysis revealed an even greater HbA1c reduction (- 0.5%) in the experimental (n=130) vs. control (n=161) patients (-1.3% vs. -0.8%; P<0.003). Further analyses of data from the STeP study have revealed improvements in several other parameters, including clinicians' intensification of treatment; depression and diabetes-related distress; and patient self-efficacy and autonomous motivation in managing their diabetes. Similar findings were seen in a pilot study by Franciosi et al. (Franciosi, Lucisano et	

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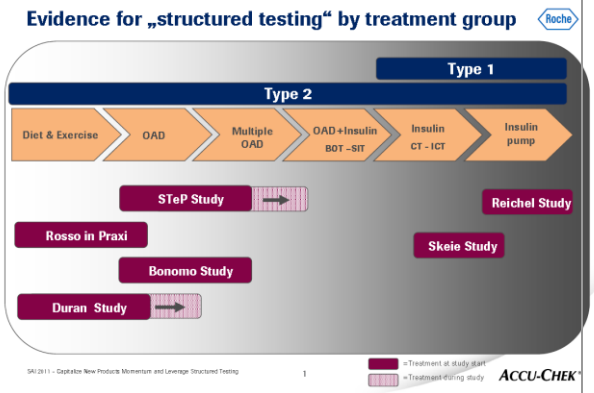
					al. 2011) evaluating the efficacy of a structured SMBG-based intervention with T2DM patients treated with oral agents. Parkin et al. have published a review article that provides more detailed descriptions of these studies (Parkin, Hinnen et al. 2009).  **Figure** 1: Evidence for "structured testing" by treatment (Roche Diabetes Care) Further studies have proven the effective contribution of structured SMBG within different treatment regimens (Skeie, Kristensen et al. 2009, Bonomo, De Salve et al. 2010, Duran, Martin et al. 2010, Kempf, Kruse et al. 2010, Reichel 2010, Kempf, Kruse et al. 2012).	
826	Roche Diabetes Care Limited	Full	28 -29	46-13	"We also found significant differences between the standard treatment guidelines (STG) and the active control group (ACG) in the frequency and intensity of the treatment change	Thank you for your feedback. The STeP trial (Polonsky 2011) has been included in the evidence review for the guideline (see section 8.3.2.2).

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					recommendations made by physicians. This suggests that when patients bring structured SMBG information to clinic visits, and when physicians know how to interpret and respond to SMBG information, timely and appropriate treatment changes are more likely to occur than in cases in which structured SMBG data are not available, as occurred in the ACG. Another possible explanation is that the treatment changes made by the STG physicians, and the resulting improvements in HbA1C, occurred because only the STG physicians were trained on a treatment algorithm and were encouraged to follow it. However the per-protocol (PP) analyses show that the glycaemic advantage occurred only among the STG patients who adhered to the intervention. Therefore, physician training alone does not sufficiently explain these findings. Additionally, the greater improvement in HbA1C over time in the STG than in the ACG occurred with less (ITT) SMBG frequency. This finding has important policy implications, suggesting that it may be appropriate to shift the current focus from SMBG quantity (testing frequency) to SMBG quality (meaningful test results that contribute to positive action), utilizing protocols that place more emphasis on when patients test and how they and their physicians organise and	

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					make clinically relevant use of the resulting data." (Polonsky 2011)	
625	Royal College of General Practitioners	Full	11	1.3.12	I think this is a very valuable, beneficial and proven intervention, and it is right that this section is included and heavily emphasised. (WS – *I will be restricting my comments mainly on the treatment of diabetic retinopathy on diagnosis*).	Thank you for your feedback.
604	Royal College of General Practitioners	NICE	11	20	I suggest to change this statement: "The outcomes are audited regularly. [2015]" **to become** "**Processes** and outcomes are audited regularly. [2015]" (AA)	Thank you for your comment. This statement as it is currently worded is taken from the recommendation which appears in the education section in the updated type 1 diabetes guideline. Although audit is a quality assessment process, the guideline development group considers the current wording of the recommendation suitable as it stands.
602	Royal College of General Practitioners	NICE	11	3,4,5	I suggest an addition to "Offer structured education to adults with type 2 diabetes and/or their family members or carers (as appropriate) at and around the time of diagnosis, with annual reinforcement and review" **to become** "Offer structured education to adults with type 2 diabetes and/or their family members or carers (as appropriate) at and around the time of diagnosis, with annual reinforcement and **review or whenever there is a need."** (AA)	Thank you for your comment. This section of the guideline was not prioritised for update. As no new evidence review has been conducted, it was not possible to make any changes to the recommendations in this section.
603	Royal College of General Practitioners	NICE	11	6	I suggest to **define what structured education is** and then list its essential components. (AA)	Thank you for your comment. Structured education has not been further defined as the recommendation included within the type 2 diabetes guideline explains what structured education is and the components it should

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						include: '*Ensure that any structured education programme for adults with type 2 diabetes includes the following components :* • *It is evidence-based, and suits the needs of the person.* • *It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.* • *It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down.* • *It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme.* • *It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.* • *The outcomes are audited regularly.*' This recommendation is also consistent with what is written in the type 1 diabetes guideline on the components of structured education.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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614	Royal College of General Practitioners	Full	12	1	If the HbA1c is over 58 **please give the patient the choice** to try harder again with weight loss instead of 'intensifying drug treatment' I have found many patients who when faced with the possible addition of a new drug will opt for, and achieve significant weight loss. Please see below evidence that diet is preferable to metformin **Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin** Diabetes Prevention Program Research Group.N Engl J Med 2002; 346:393-403February 7, 2002DOI:10.1056/NEJMoa012512 Background Type 2 diabetes affects approximately 8 percent of adults in the United States. Some risk factors — elevated plasma glucose concentrations in the fasting state and after an oral glucose load, overweight, and a sedentary lifestyle — are potentially reversible. We hypothesized that modifying these factors with a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes. Methods	Thank you for your feedback and the reference of the study that shows that people without diabetes can delay its onset with lifestyle intervention. While the guideline development group considers that diet/lifestyle interventions are paramount to diabetes management, Recommendation 1.6.8 aims to prevent clinical inertia. However, the recommendation has been slightly modified to reflect that advice about diet and lifestyle should be reinforced first, alongside drug intensification. It is envisaged that treatment selection is discussed and agreed with the patient and therefore, the individual should have the option to try harder with weight-loss interventions.

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					We randomly assigned 3234 nondiabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 34.0; 68 percent were women, and 45 percent were members of minority groups. Results The average follow-up was 2.8 years. The incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. The lifestyle intervention reduced the incidence by 58 percent (95 percent confidence interval, 48 to 66 percent) and metformin by 31 percent (95 percent confidence interval, 17 to 43 percent), as compared with placebo; the lifestyle intervention was significantly more effective than metformin. To prevent one case of diabetes during a period of three years, 6.9 persons would have to participate in the lifestyle-intervention program, and 13.9 would have to receive metformin. Conclusions Lifestyle changes and treatment	

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					with metformin both reduced the incidence of diabetes in persons at high risk. **The lifestyle intervention was more effective than metformin.** (DU)	
615	Royal College of General Practitioners	Full	12	6	Some patients learn a lot from monitoring their blood glucose after various foods – so they learn which give 'spikes' of glucose, particularly when on a new diet. (DU)	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended.
605	Royal College of General Practitioners	NICE	12	7	I suggest to add the following statement: "**Consider short-term (6-12 months) self-monitoring for adults with newly diagnosed type 2 diabetes.**" (AA)	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose (SMBG) should not be recommended. There was no evidence to indicate that SMBG in newly diagnosed patients was clinically or cost effective.
621	Royal College of General Practitioners	Full	123	14-17	Important to involve patients in setting their own targets. We very much need some tools such as decision aids to help in this discussion since the benefits of taking extra medication in the absence of symptoms may not be clear. For many the treatment burdens may outweigh the benefits. - RCGP Overdiagnosis Group	Thank you for your feedback. This suggestion will be passed to the implementation team.
607	Royal College of	NICE	123	22	HbA1c target <48mmol/mol (<6.5%) will not add any benefit to the patient—we recommend to	Thank you for your feedback. The evidence reviewed in section 8.1 in the full guideline

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	General Practitioners				make the target for this group of patients **to be <53mmol/mol (<7%)**. (AA)	showed that rising levels of HbA1c increase the risk of mortality and developing macrovascular and microvascular complications, with critical thresholds ranging from 42 to 53 mmol/mol (6.0 to 7.0%). A target of 53 mmol/mol (7%) has also been recommended for individuals who require drug intensification (see recommendation 1.6.8 in NICE version).
622	Royal College of General Practitioners	Full	123	22-30	Setting different targets under different circumstances is confusing. 7.5% does not seem to be a target in itself but acts as a trigger to a target of 7%. In view of the uncertainties around the risk/benefit balance of intensification of treatment, why not just suggest a target of 7.5% for all? Too much emphasis on trying to achieve target levels with further medication diverts attention and resources from lifestyle and BP/lipid management which have better evidence to support them. If HbA1c levels rise above 7.5%, and their individualised target is below this, it should trigger a discussion about whether or not patients wish to reconsider their target rather than automatic intensification of drug treatment. - RCGP Overdiagnosis Group	Thank you for your feedback. A target of 58 mmol/mol (7.5%) may not be appropriate for the majority of individuals. There are 2 recommended HbA1c targets: 1) 48 mmol/mol (6.5%) for people managed on diet/lifestyle or in combination with a single drug not associated with hypoglycaemia (see Recommendation 1.6.7 in NICE version) 2) 53 mmol/mol (7%) for people who require drug intensification (see Recommendation 1.6.8 in NICE version). As correctly highlighted, 58 mmol/mol (7.5%) is not a target but a threshold for intensifying drug treatment.
623	Royal College of General Practitioners	Full	123	31-34	The recognition that consideration of the relaxation of targets in the old and frail is very much to be welcomed. It would be useful to add in a comment about shared decision making at this point. - RCGP Overdiagnosis Group	Thank you for your feedback. Recommendation 1.6.5 provides guidance on involving people in decisions about individual HbA1c targets.
620	Royal College of	Full	13	Figure 1	My main concern is the advice to add repaglinide, pioglitazone or DPP-4 inhibitors as	Thank you for your feedback. The guideline development group has reflected on the clinical

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	General Practitioners				an alternative option if patients cannot tolerate metformin in patients with an HbA1c > 48 mmol/mol. Metformin has been advocated as an early therapy in Type II diabetes because it has a favorable cardiovascular outcome however none of the alternatives have shown a similar benefit and their use over sulphonylurea at this early stage should be considered carefully. Repaglinide My concerns about using repaglinide early on in the management of type II diabetes is based on both the consideration of efficacy and safety. Efficacy When Novo Norm was licensed the EMA stated that the evidence demonstrated equivalence with gliclazide. The Meta analysis however states that repaglinide is the most effective medication. This is based on few, apparently heterogeneous, studies which may potentially bias the results in favour of repaglinide. To support this suspicion I would need to know the characteristics of the included studies to determine • Differences in enrolled participants of trials: entry criteria, clinical setting, disease spectrum, baseline risk. • Differences in the interventions:	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. Full details of included studies are found in Appendix E Evidence tables. Input data into network meta-analyses are found in Appendix J.

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					dose, duration of administration, prior administration, • Differences in background treatment and management • Differences in definition or measurement of outcomes Heterogeneity of the studies. Safety Metformin is advised early in the treatment pathway because of its favourable cardiovascular status. Repaglinide's Summary of Product Characteristics (below) highlights the limited evidence base and the concern over cardiovascular risk. The cardiovascular risk was also highlighted by the EMA (below). It is essential that before advocating repaglinide as an alternative to metformin in the early stages of type II diabetes the committee must be certain there is no cardiovascular risk as this is a major co morbidity in this group. SPC "Repaglinide 2mg Tablets *Elderly* No clinical studies have been conducted in patients >75 years of age. <u>Paediatric population</u> The safety and efficacy of repaglinide in children below 18 years have not been established. No	

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					data are available.“ Acute coronary syndrome The use of repaglinide might be associated with an increased incidence of acute coronary syndrome (e.g. myocardial infarction) see sections 4.8 and 5.1.” EMA “However, in a sub group analysis an increased risk of cardio-vascular disorders were initially reported in repaglinide-treated patients compared with glibenclamide. The relative risk of serious cardiovascular adverse events ranged from 0.2 to 10.0 in various analysis with borderline statistical significance obtained in the analysis of all serious events combined (point estimate 2.2; 95%CI: 1.1-4.5).” (RB)	
626	Royal College of General Practitioners	Full	16	1.5 - # 1 & 2	This education should also make specific reference to vision, emphasising signs and symptoms of potential diabetic related ocular pathology that patients could be alerted to, along with guidance on the urgency of medical intervention needed, and education on how to access urgent ophthalmic care in those circumstances. Many patients feel that eye health is highly important to them, and raised patient awareness in this area would be highly desirable and may prevent some avoidable sight loss if eye care was sought in a timely fashion. (WS – *I will be restricting my comments mainly on the treatment of diabetic retinopathy on*	Thank you for your feedback. Education was not prioritised for update within this iteration of the guideline following a workshop with stakeholders and stakeholder consultation conducted during the scoping of the guideline. As no new evidence review has been conducted, it is not possible to make any additions or amendements to the recommendations on structured education programmes.

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					diagnosis)	
606	Royal College of General Practitioners	NICE	18	38	I suggest to add: **Consider HbA1c at Point of Care when there is a need for urgent rapid change of treatment.** (AA)	Thank you for your feedback. The guideline development group does not agree that it is necessary to provide an exhaustive list of circumstances when HbA1c should be considered.
609	Royal College of General Practitioners	NICE	22	1.6.19	The recommendation of repaglinide will I believe cause profound problems for prescribers and for people with diabetes. Repaglinide was a drug launched in the 1990's and which has had very little use. It needs to be given 3 times a day which has implications for adherence. It causes weight gain and hypoglycaemia. It has a wide dose range and there is no clear consensus as to what is the right dose. Its CVD safety profile is poorly understood. Very little repaglinide is currently prescribed in the UK so there is a lack of understanding of the agent and its use, which implies the need for widespread education of prescribers if the recommendation in this guideline is to be implemented. Repaglinide does not feature significantly in any current international guidelines. It does not significantly feature in previous NICE type 2 guideline CG 87/66 so I find it incredible that it features so prominently in this draft guideline. (RG)	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
611	Royal College of General Practitione	NICE	22-25	1.6.20	There are strong recommendations for the use of pioglitazone in this draft guideline. Prescribing of this drug has dropped in England and Wales because of the withdrawal of rosiglitazone and	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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	rs				fears over the increased risk of bladder cancer and fractures. If these pioglitazone recommendations are to be enacted there will need to be an extensive re-education programme for prescribers. Has this been understood and costed by NICE? Who will be commissioned to provide this education? (RG)	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm.
610	Royal College of General Practitioners	NICE	23	1.6.23	If repaglinide is used as initial monotherapy as per recommendation because metformin is not tolerated, but in due time a further glucose lowering agent needs to be added, repaglinide needs to be stopped and two further new agents will need to be added in a stepwise manner. This will cause huge problems for prescribers and patients and is another reason why I feel that repaglinide needs to be removed from these	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-

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					guidelines. (RG)	release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
627	Royal College of General Practitioners	Full	25	1.5 – # 85 & 86	It is reassuring that the guideline advises arranging retinal screening at or around the time of diagnosis, this is good practice and is further augmented by counselling patients on the need to attend this important screening so that attendance is not reduced by fear of outcome or non-compliance through lack of symptoms. Patients should be specifically counselled on the fact that retinopathy may exist even in the absence of symptoms, hence the importance of attending appointments. Patients should be specifically counselled on the fact that asymptomatic retinopathy, if detected early, carries a good probability of effective treatment. In the same manner as for patients, practitioners, such as GPs, could be given specific guidance on signs and symptoms that may indicate retinopathy, and guidance on how best to refer patients for further assessments, and guidance on how urgently they should act. This guidance should reflect the fact that GPs are not specialists in this area, and have limited access to diagnostic equipment. (WS – *I will be restricting my comments mainly on the treatment of diabetic retinopathy on diagnosis*)	Thank you for your feedback. It was not within the scope at this guideline update to consider the signs and symptoms of diabetic retinopathy. However, the guideline does take forward recommendations on eye screening which were published in 2009. These recommendations cover when eye screening should happen, how it should be conducted and what signs to look for. They have also been checked with the NHS Diabetic eye screening programme.
62	Royal	Full	255	4-8	I have concerns about the promotion of	Thank you for your feedback. The guideline

Type 2 diabetes (update)

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Stakeholder comments table with responses

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4	College of General Practitioners				repaglinide three times a day as the second line drug if standard release metformin is not tolerated. Clinical experience suggests that m/r metformin is well tolerated, only needs to be taken once a day, and promotes weight loss in a group of patients who are poorly compliant. I would suggest it is retained as an option in view of the benefits of metformin. - RCGP Overdiagnosis Group	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
612	Royal College of General Practitioners	NICE	26	1.6.30	Some people on GLP-1 have an excellent therapeutic response and lose a lot of weight, 3% plus but only drop their HBA1c by 0.5-0.9%. Some others have an excellent therapeutic response by dropping their HBA1c by 1.1 to 2% but only drop their weight by 1-2% of body weight. In my opinion this discontinuation recommendation ought to say a beneficial metabolic response (a reduction of 1% HBA1C) OR a weight loss of at least 3% of initial body weight in 6 months. (RG)	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
618	Royal College of General Practitioners	Full	56	37	'**Low-fat dairy produce'** – I am unaware of any quality evidence that even butter itself is bad, never mind full-fat yoghurt. I wonder what supports this statement. Increasingly The BMJ is drawing our attention to	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.

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					the lack of good evidence behind the saturated fat advice. See just one example below - it's the trans fats we are more certain cause disease **Saturated fat is not the major issue** BMJ 2013; 347 doi: http://dx.doi.org/10.1136/bmj.f6340 (Published 22 October 2013) "Saturated fat has been demonised ever since Ancel Keys's landmark "seven countries" study in 1970.2 This concluded that a correlation existed between the incidence of coronary heart disease and total cholesterol concentrations, which then correlated with the proportion of energy provided by saturated fat. But correlation is not causation. Nevertheless, we were advised to cut fat intake to 30% of total energy and saturated fat to 10%. The aspect of dietary saturated fat that is believed to have the greatest influence on cardiovascular risk is elevated concentrations of low density lipoprotein (LDL) cholesterol. Yet the reduction in LDL cholesterol from reducing saturated fat intake seems to be specific to large, buoyant (type A) LDL particles, when in fact it is the small, dense (type B) particles. (DU)	
619	Royal College of General Practitioners	Full	56	42	'Set a weight-loss target of 5-10%' YES great to emphasise this. I have often seen a 10% weight loss dramatically improve diabetic control. (DU)	Thank you for your feedback.

Type 2 diabetes (update)

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Stakeholder comments table with responses

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616	Royal College of General Practitioners	Full	General	Figures 1,2,3	Please don't assume that just because they have been counselled about the benefits of weight loss in the past it is not worth offering the patient the chance to loose weight BEFORE *intensifying drug treatment* as these figures suggest. Too many patients will end up on drugs without being given the opportunity to help themselves. (DU)	Thank you for your feedback. The algorithms have been simplified been simplied to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, it highlights the need to reinforce diet and lifestyle interventions throughout the care pathway.
608	Royal College of General Practitioners	NICE	General	General	I recommend to always use the format of (…mmol/mol (..%)) whenever needed rather than using ..mmol/mol some time with or without (..%) for HbA1c. (AA) The SGLT2 inhibitors have each received a NICE Technical Appraisal, but they are only referred to in footnotes in the glycaemic lowering sections of the guideline. Surely they should be included in the NICE guideline recommendations, treatment algorithms and pathways in line with the recommendations of their individual TA's. It would seem that NICE has a lack of clarity about how recommendations from TA's should be dealt with in Clinical guidelines. There have been TA's on some GLP-1 agents such as liraglutide and lixenatide. Have the recommendations of these TA's been included in the guideline? There seems to have been a lack of consistency at NICE over the past 10 years in deciding which new glucose lowering drugs receive a TA	Thank you for your feedback. HbA1c units have been reported as mmol/mol (%) in the guideline text. Findings from studies displayed in tables are reported in original published units, typically percentage (%). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. This guideline updates and replaces NICE technology appraisal guidance 203 (liraglutide) and NICE technology appraisal guidance 248 (exenatide prolonged-release).

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					and which will be dealt with in a guideline. Has NICE now got a clear policy on this? In my opinion the lack of integration of TA results for new glucose lowering medications into this guideline undermines the credibility of NICE processes. (RG) – editorial attached separately in PDF	
613	Royal College of General Practitioners	Full	General	General	Disappointing lack of emphasis on the prevalence and impact of co-morbid depression on people with diabetes. (CC) – supporting papers are attached separately in PDF. The guideline is extremely long and highly complex. It is unrealistic for a "normal" GP to read through in its totality. Emphasis should be made on a digestible short summary that encapsulates the most important points. The guideline is more suited to secondary rather than primary care where the vast majority of diabetes consultations take place. (DM)	Thank you for your feedback. It was not within the scope of the guideline to consider formal psychological support or psychiatric assessment for people with type 2 diabetes. However, NICE recognises that the emotional impact of living with diabetes is an important issue. The NICE pathway on diabetes will link to recommendations on depression in adults with a chronic physical health problem and also the NICE guidance on patient experience in adult NHS services. NICE anticipates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. This function links all related NICE guidance on a topic area and should assure quick navigation between recommendations on type 2 diabetes and also related NICE guidance on depression.
617	Royal College of General Practitioners	Full	General	General	I cannot find anywhere an acknowledgment that significant weight loss could mean that a patient could actually come off medications. Over the past year, ten of my patients have come off all their diabetic medications after loosing an	Thank you for your feedback. This specific issue was not a subject of an evidence review. The guideline development group has consistently reiterated in the guideline the importance of reinforcing diet and lifestyle interventions. NICE

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					average of 10Kg weight. Many of the outcomes in the studies were about HbA1c levels rather than true morbidity or mortality. Surely this surrogate marker is not enough to make so many of our patients take medication? (DU) I have **concerns about the evidence base for metformin**: please see **Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials** Rémy Boussageon, Irène Supper, Theodora Bejan-Angoulvant.. PLOS.Published: April 10, 2012•DOI: 10.1371/journal.pmed.1001204 **Methods and Findings** This meta-analysis of randomised controlled trials evaluated metformin efficacy (in studies of metformin versus diet alone, versus placebo, and versus no treatment; metformin as an add-on therapy; and metformin withdrawal) against cardiovascular morbidity or mortality in patients with type 2 diabetes. We searched Medline, Embase, and the Cochrane database. Primary end points were all-cause mortality and cardiovascular death. Secondary end points included all myocardial infarctions, all strokes, congestive heart failure, peripheral vascular disease, leg amputations, and microvascular complications. **Thirteen randomised controlled trials (13,110 patients)** were retrieved; 9,560 patients were given metformin,	also has a guideline on the identification, assessment and management of obesity in adults and children which includes recommendations on bariatric surgery, diet, physical activity and behaviourial interventions to assist in weight loss.

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					and 3,550 patients were given conventional treatment or placebo. Metformin did not significantly affect the primary outcomes all-cause mortality, risk ratio (RR) = 0.99 (95% CI: 0.75 to 1.31), and cardiovascular mortality, RR = 1.05 (95% CI: 0.67 to 1.64). The secondary outcomes were also unaffected by metformin treatment: all myocardial infarctions, RR = 0.90 (95% CI: 0.74 to 1.09); all strokes, RR = 0.76 (95% CI: 0.51 to 1.14); heart failure, RR = 1.03 (95% CI: 0.67 to 1.59); peripheral vascular disease, RR = 0.90 (95% CI: 0.46 to 1.78); leg amputations, RR = 1.04 (95% CI: 0.44 to 2.44); and microvascular complications, RR = 0.83 (95% CI: 0.59 to 1.17). For all-cause mortality and cardiovascular mortality, there was significant heterogeneity when including the UK Prospective Diabetes Study subgroups (I^2 = 41% and 59%). There was significant interaction with sulphonylurea as a concomitant treatment for myocardial infarction (p = 0.10 and 0.02, respectively). **Conclusions** **Although metformin is considered the gold standard, its benefit/risk ratio remains uncertain.** We cannot exclude a 25% reduction or a 31% increase in all-cause mortality. We cannot exclude a 33% reduction or a 64% increase in cardiovascular mortality. Further studies are needed to clarify this situation. (DU)	
62	Royal	Full	Gene	Gen	The subsequent recommendations in the	Thank you for your feedback.

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8	College of General Practitioners		ral	eral	guidelines are concerned with the procedures within a screening service, and this activity is usually undertaken by providers, and not GPs. However, the recommendations made here seem relevant and appropriate. Patient education on diabetic screening is important and is recommended in the guideline; this should be tailored to patient's individual circumstances. Patient education should include the rationale and importance for attending screening appointments. Primary care practitioners should refer patients on diagnosis of diabetes to a retinal screening programme, unless there is good justification not to, such as in terminal end of life patients. This is recommended in the guidelines. There is scope in this guideline to help primary care practitioners with what to look out for in diabetic retinopathy, and how to refer for further assessment. (WS)	
868	Royal College of Nursing	NICE	11 and throughout	1	Why are % readings being included in this document? HbA1c measurement switched to mmols/mol in 2011 which is referenced in point 1.6.2 and laboratories only present results in mmol/mol. The continued used of % four years after the change is promoting the use of outdated terminology.	Thank you for your comment. To ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that they remain within the guidance. Therefore both the mmols per mol and percentage readings have been retained.
836	Royal College of	Full	11	1	Why are % readings being included in this document?	Thank you for your comment. To ensure NICE guidance is as clear as possible to the greatest

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	Nursing		- 12 and throughout		HbA1c measurement switched to mmols/mol in 2011 which is referenced in point 1.6.2 and laboratories only present results in mmol/mol. The continued used of % four years after the change is promoting the use of outdated terminology.	number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that they remain within the guidance. Therefore both the mmols per mol and percentage readings have been retained.
840	Royal College of Nursing	Full	12	18	There is no mention that if patients are symptomatic a sulphonylurea should be commenced (page 20 line18, point 46).	Thank you for your feedback. Recommendation 46 in the full guideline (or 1.6.15 in the NICE version) states: "*If an adult with type 2 diabetes is symptomatically hyperglycaemic, consider insulin (see recommendations 63–65) or* ***a sulfonylurea****, and review treatment when blood glucose control has been achieved.*"
842	Royal College of Nursing	Full	12	19	Reference is made to tolerability of pioglitazone but not its efficacy – we consider that whilst in patients with significant insulin resistance this drug can have a marked effect on their HbA1c, on other patients it will have no impact and therefore should be stopped prior to a further medication being commenced.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
843	Royal College of	Full	12	21	If Repaglinide has been effective but the natural deterioration in glycaemic control occurs due to	Thank you for your feedback. The guideline development group has reflected on the clinical

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	Nursing				the progressive nature of type 2 diabetes and an additional drug is required but Repaglinide has to be stopped prior to commencing the additional treatment would need to be replaced with an equivalent dose of sulphonylurea first to prevent a marked deterioration in glycaemia control. This is complicating the treatment pathway and introducing high risk of significant periods of marked deterioration of control.	evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The health economic model had annual cycles and was not structured to consider short term deterioration in control that could occur when switching or intensifying treatment options.
841	Royal College of Nursing	Full	12	4, 19-23	The initial dose of Repaginide is 0.5mg titrated every 2 weeks to maximum single dose of 4mg and total daily dose of 16 mg (4mg ODS) to facilitate this dose titration regular blood glucose monitoring will be required to identify need for dose titration of frequency of dosing. The need for 3-4 times daily dosing will have negative impact on adherence and goes against the recommendations in the **medicines adherence guidance** referenced on page 12 line 4 which states 1.1.22 *"Be aware that patients may wish to minimise how much medicine they take." For many patients this relates to not only the number of different tablets they take but the actual number of tablets they take.* ***1.2.8*** *"Simplifying the dosing regimen".*	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.

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					Repaglinide has a complicated dosing regimen needing to be taken QDS for the maximum prescribable dose to be given and if 4mg is given once daily instead of 2mg BD or 1mg/1mg/2mg to spread effect across the day to address blood glucose profile can cause significant hypoglycaemia - tablets are 0.5mg,1mg and 2mg tablets with the need for different doses at different meals - a single dose of 4mg if applicable which is rare is at least 2 tablets maximum dose id 8 tablets daily. If doses are increased in the 0.5 mg dose increments recommended patients could be using 2 or 3 different dose of tablets.	
844	Royal College of Nursing	Full	13/14		**Initial therapy algorithm** % results should not be included in the algorithm There appears to be no mention in this algorithm that a Sulforylurea (SU) should be commenced if symptomatic see page 20 line 18 point 46. % results should not be included in the algorithm (see first point). Sodium Glucose Transport 2 (SGLT 2) need to be included in this algorithm or it will be of no benefit to clinicians. Patient preference mentioned in relation to Repaglinide and Dipeptidyl peptidase-4 (DPP-4)	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that both mmols per mol and percentage readings are included. The algorithms have been simplified to a single A4 page and rescue treatment with insulin or a sulfonylurea added. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug

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					(DPPIV) and SU but not for pioglitazone. If Metformin contraindicated then all drug groups should be an option based on contraindications or patient preference.	therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. **The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.**
845	Royal College of Nursing	Full	14		**First Intensification algorithm** % results should not be included in the algorithm. Patient preference only appears to be an option	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and

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					if Metformin contraindicated as first line therapy. It is not clear on the algorithm that Repaglinide should be stopped if commenced as first line at this point. Although Pioglitazone may have been declined as initial therapy for weight reasons it may be preferable to patients over an SU at first intensification but not present as an option for those on DDP IV. SGLT 2s need to be included in this algorithm or it will be of no benefit to clinicians. There seems to be nothing about stopping any of the medication if ineffective - DPPIV and Pioglitazone does not have a positive impact on all patients HbA1c - if no response it should be stopped and alternative treatment started rather than an addition of third treatment.	people with diabetes, many of whom may still be familiar with percentages, it is important that both mmols per mol and percentage readings are included. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The algorithms have been simplified to a single A4 page with a footnote specifically stating that repaglinide would need to be stopped and switched at first intensification. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people

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						who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The guideline includes a generic recommendation 1.1.1 (NICE version) that states "…*Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.

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846	Royal College of Nursing	Full	15		**Second Intensification algorithm** % results should not be included in the algorithm. This looks like patients on Metformin and DPPIV have to go straight to insulin. There does not appear to be an option to add in SU. Tolerated included but not efficacy. There seems to be nothing about stopping any of the medication if ineffective - DPPIV does not have a positive impact on all patients HbA1c - if no response it should be stopped and an alternative treatment considered rather than addition of insulin. SGLT 2s need to be included in this algorithm or it will be of no benefit to clinicians. The insulin flow looks like it should go Neutral Protamine Hagedorn (NHP) insulin change to detemir change to glargine change to Biphasic mix- detemir and Glargine should be a box together as an alternative to NHP Biphasic mix should be linked to HbA1c - as in page 23 line 25 What is the difference between Biphasic or other pre-mixed insulin – need to use biphasic or pre-mixed consistently.	Thank you for your feedback. Regarding the units of measurement for HbA1c, to ensure NICE guidance is as clear as possible to the greatest number of professionals and people with diabetes, many of whom may still be familiar with percentages, it is important that both mmols per mol and percentage readings are included. **At second intensification, the guideline development group has recommended the following for people who can take metformin: metformin+pioglitazone+sulfonylurea, metformin+sulfonylurea+DPP-4 inhibitor and starting insulin-based treatments; and for people who cannot take metformin: starting insulin-based treatments.** The guideline includes a generic recommendation 1.1.1 (NICE version) that states "…*Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic

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						combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. The algorithms have been simplified to a single A4 page with detailed information on insulin-based treatments. Term has been changed to "pre-mixed (biphasic) human insulin" for consistency.
847	Royal College of Nursing	Full	18	38 and 40	'At target' should be used rather than *"stable"*	Thank you for your feedback. The phrase "stable" has been retained.
848	Royal College of Nursing	Full	19	12-13	RECOMMENDATION TO USE REPAGLINIDE goes against the recommendations in the **Medicines Adherence guidance** referenced on page 12 line 4 which states 1.1.22 *"Be aware that patients may wish to minimise how much medicine they take." For many patients this relates to not only the number of different tablets*	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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					they take but the actual number of tablets they take. ***1.2.8*** *"Simplifying the dosing regimen".* Repaglinide is a complicated dosing regimen needing to be taken four times a day for the maximum prescribable dose to be given and if 4mg is given once daily instead of 2mg twice daily or 1mg/1mg/2mg to spread effect across the day to address blood glucose profile can cause significant hypoglycaemia - tablets are 0.5mg,1mg and 2mg tablets with need for different doses at different meals - a single dose of 4mg if applicable which is rare is at least 2 tablets maximum dose id 8 tablets daily. If doses are increased in the 0.5 mg dose increments recommended, patients could be using 2 or 3 different dose of tablets.	The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
869	Royal College of Nursing	NICE	19	25	Have you considered the risk of hypoglycaemia in people with diabetes trying to attain these targets (53mmol/mol if on insulin, Repaglinide or sulphonylureas?	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
849	Royal College of Nursing	Full	19	43	All drivers on Repaglinide will need to monitor blood glucose level.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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						pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
851	Royal College of Nursing	Full	20	46	This point is completely missed from the algorithm.	Thank you for your feedback. The algorithm has been simplified to a single A4 page, including rescue treatment with insulin or sulfonylurea illustrated.
850	Royal College of Nursing	Full	20	6	*"Consider short term"* should be replaced with 'commence self-monitoring for the duration of treatment with....'	Thank you for your feedback. The phrase "short-term" has been kept in the amended recommendation: "*Consider short-term self-monitoring of blood glucose levels (and review treatment as necessary):* • *when starting treatment with oral or intravenous corticosteroids* ***or*** • *to confirm suspected hypoglycaemia.*"
870	Royal College of Nursing	NICE	21	1.6.13	This could mean most people with Type 2 diabetes mellitus on SUs or Repaglinide who drive will need to test.	Thank you for your feedback. The recommendation notes that individuals on oral medications that may increase the risk of hypoglycaemia while driving or operating machinery should be considered for self-monitoring as per the DVLA guidance.
871	Royal College of Nursing	NICE	21	1.6.13	Suggest *"Consider"* be replaced with 'commence self-blood glucose monitoring for the duration of treatment.....'	Thank you for your feedback. As there was no evidence to suggest that patients on corticosteroids should self-monitor, a strong

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					Diabetes and steroids - Please check the Joint British Diabetes Societies (JBDS) management of hyperglycaemia for people taking gluco-corticosteroids - all should be about blood glucose testing.	recommendation of "Commence" cannot be applied and therefore the term "Consider" has bene used.
872	Royal College of Nursing	NICE	21	1.6.16	1.6.16 this implies that Metformin has to be commenced on all individuals even if they have a low BMI.	Thank you for your feedback. Metformin can be offered to individuals whose blood glucose levels are inadequately controlled by diet and lifestyle interventions only, irrespective of BMI.
852	Royal College of Nursing	Full	21	16	The need to stop Repaglinide when first intensification is needed and the complex dose titration is delaying the important achievement of excellent glycaemic control to enable individuals to benefit from the protection offered by the metabolic memory.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
853	Royal College of Nursing	Full	21	28	What if pioglitazone has no impact on HbA1c where is the guidance to stop it?	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination

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						options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
854	Royal College of Nursing	Full	21	36	What if DPPIV has had no impact on Hba1c where is the advice to stop it?	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
855	Royal College of Nursing	Full	21	57	What if SU has had no impact on Hba1c where is the advice to stop it?	The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
873	Royal College of Nursing	NICE	22	1.6.19	Please state where Metformin sustained release fits in with this?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has

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						recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
874	Royal College of Nursing	NICE	22	1.6.21	Please state patients who would be at increased risk of hypoglycaemias and or weight gain when using the SU - Also please advise on the use of a SGLT-2 inhibitor and where it sits in this pathway?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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856	Royal College of Nursing	Full	22	40	What constitutes specialist care setting?	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
874	Royal College of Nursing	NICE	23	1.6.22	3rd bullet - Is the drug with the lowest acquisition cost the most effective?	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
875	Royal College of Nursing	NICE	23	1.6.23	Where do SGLT-2 Inhibitors fit in or GLPI receptor agonists?	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update

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						TA guidance. Please see recommendations 1.6.29, 1.6.30 and 1.6.31 in the NICE version for the position of GLP-1 mimetics.
876	Royal College of Nursing	NICE	23	1.6.23	Not clear Repaglinide is to be stopped.	Thank you for your feedback. As stated in recommendation 1.6.23 (in NICE version) "*When switching from repaglinide to any of these combinations, introduce the 2 new medicines in a stepwise manner, checking for tolerability of each*", repaglinide should be stopped and switched.
878	Royal College of Nursing	NICE	24		The use of SGLT-2s – It would be helpful to be more specific about the use of these agents in reducing HbA1c and in reducing weight. Healthcare professionals will not want to keep checking all the different guidelines as they have limited consultation time.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
877	Royal College of Nursing	NICE	24	1.6.24	Use of Pioglitazone – There should be provisos around it use such as: 'Or if the individual has heart failure or previous history of bladder cancer or is post-menopausal or where an increase in weight is undesirable.'	Thank you for your feedback. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
879	Royal College of Nursing	NICE	26	1.6.29	Are they all equally effective? There is evidence that the cheapest is not always the most effective.	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see

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						MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
880	Royal College of Nursing	NICE	26	1.6.30	If the patient has lost the weight and not reduced HbA1c there are still health benefits re cardiovascular that should be taken into account.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
881	Royal College of Nursing	NICE	26	1.6.31	Specialist care setting needs to be defined in relation to suitably trained healthcare professional (HCP) not location. Suitably trained HCPs in intermediate care or enhanced practice are capable of caring for these individuals and in many service design models do in fact care for these people, without involvement of secondary care which would be historically considered to be specialist care.	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
882	Royal College of Nursing	NICE	26	1.6.32	Suggest include insulin safety advice and driving advice in this section.	Thank you for your feedback. Referral to DVLA guidance has been added to the recommendation.
88	Royal	NICE	27	1.6.3	This reads as if all other oral hypoglycaemic	Thank you for your feedback. The

Type 2 diabetes (update)

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3	College of Nursing			3	agents should be stopped yet for NPH once daily or other basal insulin to be effective it will need to be used in combination with other hypoglycaemic agents in addition to Metformin - if this recommendation means that insulin must only be used with Metformin then the insulin recommendations will need to be amended.	recommendation (1.6.32, NICE version) has been amended to: "*When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.*" for greater clarity.
884	Royal College of Nursing	NICE	27	1.6.34	2nd bullet point: Where does Degludec fit with this?	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec–metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec–metformin, and subsequently it does not appear in the algorithm.
885	Royal College of Nursing	NICE	30	1.7.11	There needs to be specific clear guidance on diabetes and chronic kidney disease (CKD) in this document and especially around screening and monitoring; and also the use of oral diabetes medications where dose reduction or use with caution or non-use depending on CKD function varies between the same class of medications.	Thank you for your feedback. The recommendations on chronic kidney disease have been updated by the recently published guideline on Chronic Kidney Disease. NICE anticipates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. This function links all related NICE guidance on a

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					Where is the guidance on when to refer to specialist care? HCPs need this guidance in this document for time saving reasons and ease of access as thereby limit the risk of some missing to pull out the recommendations from the renal guidance.	topic area and should assure quick navigation between recommendations on type 2 diabetes and chronic kidney disease.
837	Royal College of Nursing	Full	50	12	The guideline does not seem to have made a specific recommendation on review by a registered dietician – It makes one statement - *'it is **usual** that a registered Dietician plays a key role* ….' We suggest that a strong recommendation on the role of the Registered Dietician is required and should be specified in this guideline.	Thank you for your feedback. This section of the guideline was not prioritised for update, which means no new evidence review has been undertaken. Therefore it is not possible to make any changes to the text of this chapter to suggest any change to practice or to specify the involvement of different healthcare professionals.
838	Royal College of Nursing	Full	50	18 - 22	Smoking cessation is mentioned at the beginning of this section which is specific to "dietary advice". It is not clear why the statements relating to smoking cessation are included here. They seem out of place in this section.	Thank you for your feedback. It was not within the scope of the guideline to update this section of the guideline. Therefore, following NICE process, this section from the previous iteration of the type 2 diabetes guideline has been retained in the updated guideline.
839	Royal College of Nursing	NICE FULL	50 12	table 5	*"Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon*" has been removed from the guidance but continues to form part of the curriculum for the structured education process recommended in 1.3.1	Thank you for your feedback. The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of plasma glucose should not be recommended. NICE anticipates that diabetes education and curriculums for healthcare

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						professionals will change and continue to develop based on the latest review of the best available evidence.
861	Royal College of Nursing	Full	56	19	The guideline also states that "*low carbohydrate diets were noted to be of unproven safety in the long run…and could not be endorsed"* – surely some reference should be made here to the benefits of a reduction in intake, particularly of those diets high in fat to help with glycaemic control and weight management.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
862	Royal College of Nursing	Full	56	22 - 25	The guideline also talks about '*control of saturated and trans fatty acid intake'* – this is not specific enough. We consider that there should be a recommendation on the replacement of these fats with mono and poly unsaturated fat and to reduce overall intake to aid weight loss	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
863	Royal College of Nursing	Full	56	29	This section concludes with a recommendation to *"Provide individualised and on-going nutritional advice from a healthcare professional with specific expertise and competencies in nutrition'*. This re-visits the ambiguity of the Quality of Outcomes Framework (QOF) indicator regarding a 'suitably competent professional' as it is difficult to assess. The right outcome can only be ensured if the services of a registered dietician is engaged - who will assess this competence, and ensure that the advice given at primary care level is current and accurate.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
860	Royal College of Nursing	Full	56	6	Some of the terminology used here seems confusing such as *"…high levels of free carbohydrate in foods…"* which we consider	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not

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					means 'sugar' rather than complex carbohydrates?	possible to make changes to this section.
864	Royal College of Nursing	Full	57	14	Section 5.1.6 (14) advises that *"…limited substitution of sucrose-containing foods for other carbohydrates is allowable but they should take care to avoid excess energy intake."* - Again, we consider that this recommendation is confusing and could be worded with clearer wordings, for example – '…replacing foods high in sugar with more complex carbohydrates such as fruit, cereals, bread etc. will help to improve glycaemic control and reduce weight.'	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
833	Royal College of Nursing	NICE Full	General	General	The Royal College welcomes the opportunity to comment on this draft guideline. The member of the RCN Diabetes Nursing Forum reviewed and commented on this draft guideline document on behalf of the RCN.	Thank you for your feedback.
834	Royal College of Nursing	NICE Full	General	General	These days when every other news article comments on the problems of the increase in prevalence of obesity in the population we wonder why these guidelines recommend drugs which could potentially cause weight gain? There is so much evidence about the true cost of diabetes in terms of money and other the cost to the NHS and patients. We consider that all these should be factored in and the guideline should be more patient centred. We consider that the NHS should invest more	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where

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					on effective drugs to get tighter control on diabetes and achieve good outcomes.	metformin is contraindicated or not tolerated. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
835	Royal College of Nursing	NICE	General	General	This guideline seems to have gone back in time, seems to have ignored empirical research and has made it clear that it is purely a cost saving measure, which seems to focus on the use of cheap off patent drugs to keep cost down. It does not seem to have factored in and recognise the cost of the hypoglycaemias and weight gain to the patient; and increasing patients' risks of depression leading to further weight gain. It does not seem to have fully taken into consideration the patients' choice in decisions about how their condition could be best managed.	**Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).**
88	Royal	NICE	Gene	Gen	This guideline is at odds with all other	Thank you for your feedback. Recommendations

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6	College of Nursing	Full	ral	eral	international and some UK specific guidance. The pathways are confusing as is the treatment algorithms in the full guidance and will not be helpful to healthcare professionals working with individuals with diabetes. The use of medications which can lead to hypoglycaemia or weight gain without deference to clear safety information is concerning as is the unclear guidance on glycaemic targets – The American Diabetes Association (ADA) information regarding agreed targets depending on clinical need, co-morbidities and other factors such as motivation, duration of diabetes is clear and concise. It would be beneficial if this was in this UK guideline. Primary care practitioners may be unfamiliar with Repaglinide and without significant education which will need to be funded as unlikely to be supported by companies producing Repaglinide as off patent, could result in a significant increase in hypoglycaemia or periods of poor control due to poor titration and need to stop at second intensification. The failure to include SGLT2 in recommendations means that this guideline in relation to glycaemic management will be incomplete and the algorithms will be of no clinical benefit to healthcare professionals and	are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of

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					will need to be rewritten locally to reflect all guidance. As these draft recommendations stand justifying the conclusion made and teaching and training in particular for none specialist clinicians when the guidance is not in sync with other international recommendations would be challenging and probably inappropriate.	drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
857	Royal College of Nursing	Full	General	General	We would urge NICE to consider the significant impact poly pharmacy will have on this population of patients. The increase likelihood of using multiple agents and changes in prescriptions when patients cannot tolerate Pioglitazone or adhere to Repaglinide should be considered.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where

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						metformin is contraindicated or not tolerated. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
858	Royal College of Nursing	Full	General	General	Of the four research trials looked at, one seems irrelevant as it looked at the impact of Sibutramine which has not been licensed for at least four years in the UK. It is not clear why this has been used as evidence for this guideline.	Thank you for your feedback. The evidence on sibutramine is included in a section on the guideline which has not been updated by an evidence review and has been retained from the previous iteration of the guideline. The previous iteration of the guideline was developed before sibutramine had its license for use in the UK removed.
859	Royal College of Nursing	Full	General	General	From the other three studies it is clear that weight loss contributes to improved glycaemic control, however there is no mention of GLP-1 therapy or SGLT-2 therapy as being a sensible option for treatment or that Gliclizide and Repaglinide have the well-known side effect of weight gain – it would be helpful to know how this would be help in the long term management of the condition?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice

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						around which pharmacological interventions are appropriate for consideration. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance. GLP-1 mimetics are recommended at second intensification. Based on the updated evidence review and health economic analysis, the guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their

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						associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from CG87.
865	Royal College of Nursing	Full	General	General	The cost of treating hypoglycaemia (including ambulance services/hospital admissions/Quality of Life etc.) must surely be a consideration when prescribing oral diabetic drugs, particularly when there are other drugs that pose a lesser risk to individuals. Using drugs which cause hypoglycaemia also of course has an economic impact with the need to carry out blood glucose monitoring.	Thank you for your feedback. NHS costs relating to severe hypoglycaemic episodes were fully considered in the health economic modelling (see full guideline 8.4.3). These included estimates of the proportion of severe hypoglycaemic episodes that required GP admissions, ambulance call outs, A&E attendance and/or hospital admissions.
866	Royal College of Nursing	Full	General	General	The changes to the pharmacological management in particular are too major to be accepted. Management of type 2 diabetes is fraught with the heterogeneity of the disease and this new complex model for therapy management is open to confusion and inappropriate choice of agent.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
832	Royal College of	Full	General	3-4	The sentence should include intravitreal anti-VEGF treatment / intravitreal steroid therapy (as	Thank you for your feedback. It was not within the scope of the guideline to update this section

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	Ophthalmologists		Section 9.4.1, page 289		well as the laser treatment mentioned) as these are now part of the therapeutic options for patients with diabetic macular oedema.	of the guideline. Therefore, following NICE process, this section from the previous iteration of the type 2 diabetes guideline has been retained in the updated guideline.
831	Royal College of Ophthalmologists	Full	General (but Eye section specifically is 9.4.1	General	The document does not make reference to the fibrate data from ACCORD eye study (NEJM 2010 July 15th, and Ophthalmology Dec 2014 2443-51). This assessed a subgroup of people with Type II diabetes in the ACCORD study (backing up previous data from FIELD Study) and showed that the addition of a fibrate to a statin for people with type II diabetes slowed the rate of significant progression of retinopathy (3 steps on the EDTRS grade) from 10.2% in the placebo plus statin group to 6.5% in the fibrate plus statin group at the 4 year follow-up, a reduction of 40% . The Royal College of Ophthalmologists feels that it is very important for that evidence to be considered by the guidelines team, and recommendations made concerning the use of fibrates in this group, as they feel appropriate. The action of the fibrate here is not thought to be through its lipid lowering effect.	Thank you for your feedback. It was not within the scope at this guideline update to consider the evidence for diabetic retinopathy. However, the guideline does take forward recommendations on eye screening which were published in 2009. These recommendations cover when eye screening should happen, how it should be conducted and what signs to look for. The recommendations have also been checked by the Diabetic Eye Screening Programme.
92	Royal College of Physicians of Edinburgh	Full	11	31	This section pays little reference to NICE's own Single Technology Appraisals and runs counter to the patient-centric approach of the well-established and respected joint guideline recently issued by the European Association for	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the

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					the Study of Diabetes (EASD) and American Diabetes Association (ADA), as well as common clinical practice in the UK.	appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where appropriate.
93	Royal College of Physicians of Edinburgh	Full	12	19	The recommendation to use Repaglinide as second line compared to standard sulphonylureas (or first line if Metformin is not tolerated) is surprising. This is because several of the comparators do not include large scale studies on Repaglinide and the decision to use this drug reflects a small number of trials looking at glucose lowering.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
94	Royal College of Physicians of Edinburgh	Full	12	21	The suggestion that Pioglitazone becomes a second line alternative is flawed. It is well established that it is associated with significant weight gain and there is also a concern that thiazolidinediones may be linked to adverse cardiovascular risk. Thiazolidinediones are associated with other adverse effects, including increased fracture risk, bladder cancer, weight gain and heart failure (as noted by guidance from MHRA and EMA.) For this reason their	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is

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					routine use is limited. Indeed one of the agents in this class has been removed from the UK market. On this basis, their use should not be recommended so prominently by the draft guideline. We recommend this is changed. The current convention of using DPP-4 antagonists such as Sitagliptin is preferred because it is associated with neutral effects on weight.	contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
95	Royal College of Physicians of Edinburgh	Full	13	1	The glucose-management medicine algorithms recommend the use of agents which are the subject of important safety concerns and associated with side effects such as weight gain (as above). Further, it includes some agents that are not recommended in current guidelines. Health and safety warnings pertaining to these agents have been omitted from the full guidance document altogether. The draft guideline is not reflective of common UK clinical practice, NHS England priorities and current European consensus guidelines. The new guideline could drive GPs to preferentially prescribe medicines that may have serious safety issues for some patients and limited UK clinical experience (thiazolidinediones and rapid acting insulin secretagogues). It would also encourage the use of these medicines in dual therapy combinations and there is limited clinical	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. Cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors has been included where

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					experience of these combination.	appropriate. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
96	Royal College of Physicians of Edinburgh	Full	13	1	The draft positioning of these treatment classes as suitable only when a sulphonylurea is contraindicated is fundamentally inconsistent with all existing guidance, including current NICE guidance.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
97	Royal College of Physicians of Edinburgh	Full	13	1	Rapid acting insulin secretagogues are associated with adverse events, including hypoglycemia and weight gain. Compliance/concordance is recognised as a major factor in poor medication adherence which is considered to be one causative factor in poor outcomes.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
98	Royal College of Physicians	Full	13	1	The 'Algorithm for Blood Glucose Lowering Therapy' contradicts the need for 'patient-centred care' and guides prescribers to take a	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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	of Edinburgh				very restrictive approach that does not consider the holistic needs of individuals with type 2 diabetes. The algorithm is inconsistent as to whether alternative treatments are acceptable in the context of clinician preference, patient preference, or only where there is a specific contraindication. The apparent focus on short-term drug acquisition costs fails to acknowledge the longer-term impact of the effective use of medicines in reducing avoidable complications associated with type 2 diabetes. The implementation of the algorithm in its current form will obstruct efforts to reduce these costs and improve overall outcomes for individuals with type 2 diabetes. The 'Algorithm for Blood Glucose Lowering Therapy' should be revised so that it clearly supports clinicians to deliver an individualised 'patient-centred care' approach to type 2 diabetes management. The rigidity of the treatment pathway is inconsistent in relation to both stated goals and recommended treatments.	pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
99	Royal College of Physicians of Edinburgh	Full	13	2	Cost-effectiveness modelling for NICE excludes adverse events and only takes HbA1c into consideration. This is misleading and does not take into consideration holistic care and the potential long-term impact on persons living with	Thank you for your feedback. Cost-effectiveness modelling for NICE included dropouts due to adverse events, weight and hypoglycaemia as well as HbA1c (see 8.4.3 in the guideline).

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					diabetes.	
100	Royal College of Physicians of Edinburgh	Full	13	2	Focus on drug acquisition cost is retrograde, and is inconsistent with NHS England and the Department of Health's medicines optimisation agenda.	Thank you for your feedback. The health economic modelling considered both costs and quality of life impacts of long-term complications (in part driven by changes in HbA1c), hypoglycaemia rates, treatment-related weight changes as well as drug acquisition and management costs (see 8.4.3 in the full guideline).
101	Royal College of Physicians of Edinburgh	Full	13	2	If implemented, the algorithms would discourage and delay the use of innovative, cost-effective medicines within the NHS and there is a danger of the NICE guideline being ignored and therefore not functioning as a 'guideline'. The NICE guideline has the opportunity to increase the availability and use of the best branded medicines and most innovative treatments, at minimal cost. It should allow clinicians to have greater flexibility to prescribe more expensive, non-generic medicines. Some of the costs of prescribing are underwritten by the pharmaceutical industry.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
102	Royal College of Physicians of Edinburgh	Full	24	1	The draft guideline excludes the recently published evidence that supports using GLP-1 agonists in conjunction with basal Insulin to achieve improved glycaemic control with less hypoglycaemia. Furthermore, it does not recognise current widespread use of GLP-1 agonists in conjunction with basal Insulin in UK clinical practice.	Thank you for your feedback. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics in combination with basal insulin were not identified at the cut off search date of June 2014. Any studies published after this date could not be included in this update.

Type 2 diabetes (update)

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103	Royal College of Physicians of Edinburgh	Full	34	26	This methodology may not reflect current practice of viewing overall benefit/risks in favour of measurements which concentrate on glycaemic control.	Thank you for your feedback. Other outcomes besides glycaemic control have been considered in the guideline.
104	Royal College of Physicians of Edinburgh	Full	35	34	We welcome this recognition of the detrimental impact that hypoglycaemia has on patients' quality of life.	Thank you for your feedback.
105	Royal College of Physicians of Edinburgh	Full	56	2	The recommendations appropriately make much of the importance of diet and exercise in supporting glycaemic control, but do not suggest changing current practice.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
106	Royal College of Physicians of Edinburgh	Full	56	6	Longer-term trials need to be undertaken to test the long-term efficacy and safety of low carbohydrate diets.	Thank you for your feedback. It was not within the scope of the guideline to update the evidence review on dietary advice therefore it is not possible to make changes to this section.
107	Royal College of Physicians of Edinburgh	Full	General	General	We particularly commend the sections on lifestyle advice, patient education, monitoring and targets. This includes supporting and defining 'structured education'.	Thank you for your feedback.
108	Royal College of Physicians of Edinburgh	Full	General	General	The draft guideline rightly places great emphasis on the holistic care of persons with diabetes, including the importance of weight loss and of taking measures to reduce the risk of hypoglycaemia. In contrast, the glycaemic-management medicines algorithms encourage	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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					preferential use of agents proven to negatively impact on some outcomes. Newer branded medicines have demonstrated benefit in both weight loss and glucose dependent glycaemic control.	recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
298	Royal National Institute of Blind People	Full	General	General	**About the RNIB:** Royal National Institute of Blind People (RNIB) is the UK's leading charity providing information, advice and support to almost two million people with sight loss. We are a membership organization with over 13,000 members throughout the UK and 80 percent of our Trustees and Assembly members are blind or partially sighted. We encourage members to get involved in our work and regularly consult them on matters relating to Government policy and ideas for change. As a campaigning organization we act or speak	Thank you for your feedback.

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					for the rights of people with sight loss in each of the four nations of the UK. We also disseminate expertise to the public sector and business through consultancy on products, technology, services and improving the accessibility of the built environment. RNIB is pleased to have the opportunity to respond to this consultation	
299	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 feedback. NICE is bound under the Equality Act 2010 and its own equality programme to act in accordance with equality legislation and to take equality issues into account in the production of its guidance. At stakeholder consultation and at guideline consultation an equalities form has been completed and signed off to ensure that NICE and the guideline committee have taken any equality issues into account. All public bodies which use NICE guidance must also give due regard to the Equalities Act 2010 and take this into account when delivering care in line with NICE guidance.
300	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	Thank you for your feedback. NICE is bound under the Equality Act 2010 and its own equality programme to act in accordance with equality legislation and to take equality issues into account in the production of its guidance At stakeholder consultation and at guideline

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					who do not speak or read 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	consultation an equalities form has been completed and signed off to ensure that NICE and the guideline committee have taken any equality issues into account. All public bodies which use NICE guidance must also give due regard to the Equalities Act 2010 and take this into account when delivering care in line with NICE guidance. NICE also takes accessibility very seriously and all our websites adhere to WSG AA standards as much as possible. All NICE sites are tested with this as a basic standard. Where issues are highlighted, NICE looks to address these issues and are continually improving their website on an ongoing basis.
301	Royal National Institute of Blind People	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 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	Thank you for your feedback. It was not within the scope at this guideline update to consider the evidence for diabetic retinopathy. However, the guideline does take forward recommendations on eye screening which were published in 2009. These recommendations cover when eye screening should happen, how it should be conducted and what signs to look for. The recommendations have also been checked by the Diabetic Eye Screening Programme.

Type 2 diabetes (update)

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					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 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	

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					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'.	
812	Sanofi	Full	15	general	Glucagon-Like Peptide-1 (GLP-1) mimetics are extensively used in clinical practice and, according to the criteria detailed in the draft guidelines, are an appropriate treatment for a significant proportion of people with Type 2 Diabetes. Therefore it seems appropriate that GLP-1s should be represented visually in the main algorithm flow chart rather than as a footnote. Representing the class in a footnote may be seen to imply they are not considered main stream therapies and may result in appropriate patients being denied effective treatment.	Thank you for your feedback. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
81	Sanofi	Full	22	25-	The previous NICE Type 2 diabetes guidelines	Thank you for your feedback. The

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7			257	32 6-13	(CG 87) recommended the use of GLP-1 mimetic as third-line therapy in patients with a BMI ≥ 35.0 kg/m^2 in those of European descent and included the statement "with appropriate adjustment for other ethnic groups" in order to make the class available to ethnic population. This provision has been excluded from the new update. The omission of a statement regarding flexibility of BMI criteria in ethnic groups will mean patients from relevant ethnic groups may be denied appropriate treatment with GLP-1 mimetic therapy, which would be seen as a backward step with the new guideline. A study by Gray et al (2011)^2 suggested that for South Asian males, the BMI obesity cut-off equivalent to 30.0 kg/m^2 in White Europeans, would be 22.6 kg/m^2 (95% Confidence Interval 20.7 kg/m^2 to 24.5 kg/m^2). It would seem appropriate for this and any other relevant evidence to be considered, to ensure that the needs of relevant patient subgroups are fully represented within the guidelines.	recommendation has been amended to include the text "(adjust accordingly for people from black, Asian and other minority ethnic groups)" as in the previous iteration of the guideline, CG87.
813	Sanofi	Full	22 257	37, 38, 39 18, 19,	The stopping rules for the use of GLP-1 mimetics are potentially inappropriate for patients on combination treatment of insulin and GLP-1 mimetics. Such patients are difficult to treat, insulin requiring, and with advanced disease and hence expecting a reduction of 11	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the

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				20	mmol/mol (1%) in HbA_{1c} and 3% of initial body weight in 6 months may be unrealistic. An improvement in either of these parameters would likely be seen as clinically significant. By requiring both endpoints to be realised in all patients taking a GLP-1, those patients taking GLP-1s in combination with insulin who have achieved a clinically significant benefit may be taken off treatment. It would seem appropriate to clarify that the proposed stopping rules only apply when GLP-1 mimetics are used in combination with oral drugs alone.	guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
815	Sanofi	Full	22 250 254 257	40, 41 general general 21, 22	We believe that limiting the initiation of GLP-1 mimetics in combination with basal insulin to a "specialist care setting" is unclear and open to misinterpretation. The current wording may mean patients have treatment delayed due to unnecessary referrals into secondary care, or may be denied treatment. The potential for the interpretation of "specialist care setting" to mean "secondary care" could undermine the NHS drive to provide diabetes care in the community and be seen as a significant block to appropriate patients receiving these medicines if and when required. Rewording this recommendation, or emphasising that the intended interpretation relates to the expertise of the prescriber and not the physical setting where initiation takes place, may help to alleviate these potential issues.	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
81	Sanofi	Full	22	40,	The American Diabetes Association and	Thank you for your feedback. Relevant studies

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6			250 254 257	41 gene ral gene ral 21, 22	European Association for the Study of Diabetes have recently released an updated position statement on the management of type 2 diabetes[1]. The position statement states that there has been recent published evidence on the effectiveness of the combination of GLP-1 mimetics and basal insulin. The position statement also states that the evidence suggests equal or slightly superior efficacy of this combination when compared to the addition of prandial insulin, and with weight loss and less hypoglycaemia. Furthermore, the position statement recommends the use of GLP-1 mimetics or prandial insulin in uncontrolled patients who are on basal insulin with one or more oral agents and view this treatment step as a logical progression of the treatment regimen. This is in contrast to the NICE guidelines which state lack of evidence on the combination of insulin and GLP-1 mimetics as the reason behind provision of this treatment only in "specialist care setting". The contrasting nature of these two guidelines has the potential to confuse prescribers and does recognise the current widespread combined use of insulin and GLP-1 mimetics in UK clinical practice	meeting the review's selection criteria that examined GLP-1 mimetics in combination with basal insulin were not identified at the cut off search date of June 2014. Any studies published after this date could not be included in this update. Based on the updated evidence review and health economic analysis, the guideline development group noted the lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
814	Sanofi	Full	General 22	general 37, 38,	The stopping rules for the use of GLP-1 mimetics in combination with oral drugs may in some circumstances contradict the proposed new HbA_{1c} targets. The guidelines suggest that drug treatment should be intensified when HbA_{1c}	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial

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			257	39 18, 19, 20	levels rise to 58 mmol/mol (7.5%) or higher, and the HbA_{1c} target be reset to 53 mmol/mol (7%) rather than the original 48 mmol/mol (6.5%). This means that if the guidelines are followed and a patient is initiated on a GLP-1 mimetic at HbA_{1c} of 60 mmol/mol (7.6%) and their HbA1c level drops to 52 mmol/mol (6.9%), the patient would successfully meet the HbA1c target of 53 mmol/mol (7%); however, the HbA_{1c} reduction would still not be 11 mmol/mol (1%) to justify continuation of GLP-1 mimetic and hence the patient, who had achieved clinically significant benefit, may have the treatment inappropriately discontinued. Further consideration may be needed to ensure the GLP-1 stopping rules are fully compatible with the proposed new glycaemic targets.	gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. The stopping criterion for GLP-1 mimetics is "*a reduction of at least 11 mmol/mol [1.0%] in HbA1c* ***and*** *a weight loss of at least 3% of initial body weight in 6 months*". While a decrease to HbA1c target may be achieved, if this reduction is less than 11 mmol/mol (1%) and a weight loss of at least 3% of initial body weight in 6 months are not achieved, the stopping rule comes into effect.
219	Slimming World	NICE	General	General	Slimming World welcome the guideline update and have no detailed comments on the consultation	Thank you for your feedback.
915	South Asian Health Foundation	NICE	General	General	The South Asian Health Foundation has reviewed these guidelines as part of the consultation process. We recognise that the guidelines development group had major challenges. Genuine progress has been made in the attempts to stress the importance of customising treatments and targets but at the same time these need to be sensitive to the needs and safety of the individual patient. This clearly involves cultural and ethnic needs and sensitivities and given the growing importance of	Thank you for your feedback. It was not within the scope at this guideline update to review the evidence on lifestyle and dietary advice. As no evidence review has been performed, it is not possible to update these recommendations. The structured education section within the type 2 diabetes guideline was not prioritised for update in this iteration of the guideline. Therefore it is not possible to recommend specific

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					the diverse ethnic population with Type 2 diabetes in the UK this approach is welcome. On the issues of lifestyle advice, diet, patient education, monitoring and targets the new guidelines make good sense. The support and definition of "structured education" (1,2) is sensible especially when tailored to differing needs as is the suggestion that these processes should now be regularly audited and customised to the needs and preferences of patients. It would be helpful if the guidelines could make specific reference to the tailoring of structured education programmes such as DESMOND to meet the needs of south Asian patients as an example of good practice. We would also like the guideline to emphasise recommendation of structured education programmes with an evidence base as there are a number of low cost "locally modified" structured education programmes without an evidence based being promoted in some localities. On dietary advice the recommendation is to continue current practice but there is the acknowledgement which is very sensible given the limited evidence that there needs to be more research and longer term trials on the efficacy and safety of a range of differing diets which have been trialled in European populations. The guideline development group recognises	education programmes. The current recommendations on structured education within the type 2 diabetes guideline lists the essential components of structured education which commissioners locally should ensure are provided. The recommendations are based on the clinical effectiveness review and health economic modelling analysis. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. The GLP-1 mimetic recommendation has been amended to include the text "(adjust accordingly

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					the increasing cost pressures of blood glucose monitoring. The findings of well-designed trials (3) that demonstrated a failure of glucose monitoring to improve overall glycaemic control supports this approach. Applied sensitively this suggestion that monitoring in type 2 diabetes is only necessary if they are at risk of hypoglycaemia i.e. for all those on meglitinides, and sulphonylureas or insulin is justified as the cost of this activity continues to grow . The guideline group are sensible in targets taking into account the potential for hypoglycaemia setting 48 mmol/mol (6.5%) as the target but suggesting a more realistic target of 53 mmol/mol (7.0%) in people with longer duration of diabetes, including the frail and elderly and potentially those with existing CVD, when drugs that can cause hypoglycaemia are introduced. Where the new guidelines appear to deviate from the practice and experience of many clinicians working with type 2 diabetes is in the choice of drugs to intensify treatment after metformin. There appears to be an acceptance by the group that sulphonylureas are no longer the automatic second line to metformin because of weight gain and the increase of hypoglycaemia (4, 5) and the consequent need and cost for blood glucose monitoring for them to be used safely. Indeed even with monitoring	for people from black, Asian and other minority ethnic groups)". The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Consideration for adjusting BMI levels based on ethnicity has been carried forward from CG87 recommendation. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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					there are serious concerns about hypoglycaemia in the frail and elderly with reports of rises in hospital admissions and safety concerns around driving (6,7). The choice of repaglinide a short acting insulin secretagogue now hardly used in the UK as first line for those who cannot tolerate metformin and as a possible second-line combination agent appears to make little sense. It would appear that the guidelines group have been swayed by their own complex network meta-analysis and not given enough weight and scrutiny to the potential bias from the very small number of clinical trials on these drugs available for analysis. Network meta-analytical methods can result in spurious results when a small number of studies have been included within the various nodes. Moreover, there appears to have been less recognition that higher baseline HbA1c in trials can lead to false impression that some drugs are more efficacious than others and such analyses must control for baseline HbA1c. There is considerable heterogeneity in clinical effectiveness among the RCTs of repaglinide versus placebo with the benefits of repaglinide being often due to marked rises in HbA1c on placebo. There is only one study (Jovanovic 2000) (8) in which there was a reduction of 0.68%on repaglinide with an increase of 1.3 in placebo at six months and the Cochrane review	

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					(Black 2007)(9) risk of bias table did not give it a high score. The lack of efficacy and need for dosing three times daily leading to reduced concordance were contributing reasons these drugs despite extensive promotion never took off in the UK or indeed globally. Furthermore, NICE assumes in the economic analysis that the blood glucose monitoring would not be needed for repaglinide. The trials by Jovanovic(8) and Moses (10) reported that 31% and 13% of patients on repaglinide reported hypoglycaemia. Indeed in a recent meta-analysis comparing a range of anti-diabetes agents clearly shows that the risks of hypoglycaemia with repaglinide is at least as great as that with sulphonylureas with similar weight gain (11). This is no surprise since replaglinide is essentially a short acting SU. The recommendation of pioglitazone as a principle second-line agent to metformin is also contentious and appears to be driven by the fact it is now generic and inexpensive. Weight gain is a major concern with this class and in South Asians with their propensity to central obesity most clinicians avoid the glitazone class. For all their original promise the glitazones have been tainted by the cardiovascular safety issue with rosiglitazone and its subsequent withdrawal	

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					from the European market. Again on the basis of one clinical trial (12) that suggested cardiovascular benefit, the group appear to have neglected to weigh up the class effects of fluid retention and aggravated heart failure from sodium retention now known to be an effect of PPARgamma receptor activation in the kidney (13). In addition the changes in bone density and fractures are of particular concern to South Asians who may already have metabolic bone disease.. Because of their safety profile most clinicians are cautious using them and restrict them to patients for whom other drugs have not reached target or use in selected patients where insulin resistance is a major feature. The guideline group acknowledge use of GLP-1s and their potential for significant weight loss but again on economic terms are standing by the previous recommendation of only using if BMI >35 kg/m² and withdrawing if both weight loss and improved glycaemia are not achieved. While clinicians can use them at a lower BMI "where weight loss would benefit other significant obesity-related co-morbidities" the BMI cut off is too high and as obesity is defined as BMI >30 kg/m for Europeans this would be a more logical recommendation. For South Asians it is NICE has recommended that south Asians are at high risk at a much lower BMI of 23 kg/m2 and it would be valuable if this	

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					important aspect of care for this ethnic group was recognised in the recommendation by suggesting the potential to consider a lower cut-off in SAs. The short and long acting GLP1s are different in mechanisms of action and efficacy and (14,15,) and this needs to be considered in individualising patient choice but it is reasonable for clinicians to use the GLP-1s with the lowest acquisition cost given the expense of this group and the cost differences. With regard to insulin the guideline group recognise the serious nature of hypoglycaemia that is seen with intensification of insulin but continue to recommend isophane as basal insulin only changing to analogues after patients have suffered hypoglycaemia. Recent data from the HAT global study has reported south Asian people with Type 2 diabetes having the highest rates for severe hypoglycaemia. Clearly, the group recognises that longer acting analogues cause less hypoglycaemia so apart from trying to reduce cost it is difficult on grounds of patient safety and the need for patients to remain confident in their treatment to justify this approach. These safer long acting analogue insulins are first-line in type 1 that there is no justification for the continued discrimination in type 2 patients. This issue is particularly pertinent for the younger onset type 2 South Asian patients who often come to insulin earlier	

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					and for whom using analogues allows intensification with the least hypoglycaemia and best motivation. **<u>Conclusion</u>** While the South Asian Health Foundation welcomes valuable recommendations in some areas of diabetes care in these draft guidelines in the area of drug intensification after metformin the guidance seems to end up providing inconsistent advice that will not make sense to practicing clinicians. There is a danger that NICE will lose credibility and undermine many of the important principles of putting patient safety first and the excellence they are hoping to achieve in their guidance. There were very good reasons why the insulin secretagogue repaglinide has been abandoned by most clinicians in the UK. There are important safety issues around glitazones and clinicians remain extremely cautious in their use of pioglitazone. For South Asians a recognition of a lower BMI for the definition of obesity to allow the most appropriate use of a GLP-1 and the need to recognise the needs of young people Type 2 diabetes (a high proportion of whom are South Asian) who need the safest analogue insulin options should be recognised References.	

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					1. Khunti, K, Gray LJ, Skinner T et al, Effectiveness of a diabetes education and self-management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. BMJ 2012; 344:e2333.htpp//dx.doi.org /10.1136/bmj.e2333 2. Deakin TA, Cade JE, Wiliams R, Greenwood DC. Structured patient education: the Diabetes X-PERT Programme makes a difference. Diabetic Medicine 2006 23;9;944-954. htpp://dx.doi.org/ 10.1111/j.1464-1491.2006.01906.x 3. Farmer A, Wade A, Goyder E, et al Impact of self- monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 2007; 225:132.http://dx.doi.org/10.1136/bmj.39247.447431.BE 4. Viberti G, Kahan SE, Greene DA et al. A diabetes outcome progression trial (ADOPT): an international multicentre study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care 2002; 25: (10):1737-43.http://dx.doi.org/10.2337/diacare.25.10.1737	

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					5. Leese GP, Wang J, Broomhall J et al, DARTS.MEMO Collaboration. Frequency of severe hypoglycaemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003; 26:1176-1180. http://dx.doi.org/10.2337/diacare.26.4.1176 6. Rajendran R, Hodgkinson D, Rayman G. Patients with diabetes requiring emergency department care for hypoglycaemia: characteristics and long-term outcomes determined from multiple data sources. Postgrad Med Journal 2015 (in press).http//dx.doi.org/10.1136/postgradmedj-2014-132926. 7. UK Hypoglycaemia Study Group . Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007; 50;1140-1147.http:dx.doi.org/10.1007/s00125-007-0599-y 8. Jovanovic L, Dailey G, Huang WC et al.Repaglinide in type 2 diabetes:a 24- week fixed dose efficacy and safety study. Journal of Clinical Pharmacology 2000 ;40:49-57. 9.Black .Cochrane Review 2007	

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					10.Moses RG, Gomis R, Frandsen KB et al. Flexible meal related dosing with repaglinide facilitates glycaemic control in therapy naïve type 2 diabetes. Diabetes Care 2001;24:11-15 11. Phung OJ, Scholle JM, Talwar M, Coleman CL. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycaemic control, weight gain, and hypoglycaemia in type 2 diabetes. JAMA 2010; 303: 1420-28 htpp://dx.doi.org/10.1001/jama.2010.405 12. Dormandy JA, Charbonell B, EcklandDJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the Proactive study:a randomised controlled trial. Lancet 2005;366(9493):1279-1289 13.Goenka N, Kotonya C,Penny MD,Randeva HS and O'HareJP. Thiazolidenes and the renal and hormonal response to water immersion – induced volume expansion in type 2 diabetes mellitus. Am J.Physiol Endocrin metab 2008;294(4):733-739 14. Robinson LE, , Holt, TA, Rees K, Radneva H, O'Hare J.P. Effects of GLP-1 agonists on heart rate, blood pressure and body weight: Systematic review and meta-analysis BMJ Open 2013 ; 3	

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					:pii:e001986.htpp://dx.doi.org/10.1136/bmjopen-2012-001986 15. Thong KY, Gupta PS, Cull ML et al. GLP-1 receptor agonists in type 2 diabetes - NICE guidelines versus clinical practice. Br J Diabetes Vasc Dis 2014;14:52-59.htpp://dx.doi.org/10.15277/bjdvd.2014.015	
286	South Sefton CCG	Full	13	Figure 1	Metformin Modified Release has proved a useful treatment for individuals unable to tolerate standard formulation.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
287	South Sefton CCG	Full	13	Figure 1	For those who are totally intolerant of all metformin formulations the use of repaglinide is too complex to ensure concordance. This is made worse if it has to be switched to a different treatment at the first intensification.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors,

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						pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
288	South Sefton CCG	Full	13	Figure 1	Pioglitazone has a significant number of contra-indications and is not favoured due to its propensity to increase weight which is not desirable. It is important to discuss the relative benefits and harms of pioglitazone with the patient before initiating treatment. Pioglitazone tends to be slower in its onset of action and appears to give its best results in patients with a fatty liver. There is no suggestion about it being discontinued if there is no response.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). In addition, the generic recommendation 1.1.1 (NICE version) states "…*Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm.
289	South Sefton CCG	Full	13	Figure 1	DPP-4 inhibitors are suggested in the algorithm but there is no mention of SGLT-2 agonists although they are covered in the NICE Version	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug

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					of the Guidelines-i.e an element of inconsistency	therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
290	South Sefton CCG	Full	13	Figure 1	Suggest Sulphonylurea tolerated –no or not suitable ie in frail and elderly living alone and unable to monitor or contra-indicated-CKD 4 – risk of prolonged hypoglycaemia.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
291	South Sefton CCG	Full	14	Figure 2	No direction to titrate metformin or metformin MR to maximum dose(Metformin 1g tds, Metformin MR 2G daily) or the maximum tolerated dose.	Thank you for your feedback. This information is in the Summary of Product Characteristics.
292	South Sefton CCG	Full	14	Figure 2	Suggest Pioglitazone contra-indicated or not suitable.. Reasoning for example 3 holds true for this example. Discuss relative benefits and harms with patient. Consider for patients with a fatty liver if no contra-indications of which there are a few.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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						The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
293	South Sefton CCG	Full	14	Figure 2	Suggest Sulphonylurea contra-indicated or not suitable ie in elderly living alone and unable to monitor. Risk of prolonged hypoglycaemia in the elderly with CKD3b to 4.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
294	South Sefton CCG	Full	15	Figure 3	When moving from Triple therapy with oral hypoglycaemic agents or metformin and a DPP-4 the algorithm seems to suggest stopping all Oral Hypoglycaemic agents apart from metformin. Less insulin may be required resulting in a lower weight gain if agents with no clinical effect are removed. It does not make allowance for patients with CKD3b or 4 in which case it would be appropriate to maintain a DPP-	Thank you for your feedback. The guideline development group has recommended that: "*When starting insulin therapy, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.*"

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					4 at an appropriate dose.	
295	South Sefton CCG	Full	15	Notes	For a patient who has had a trial of metformin a sulphonylurea and a glucagon-like peptide-1 with normal renal function ie eGFR >60 then a trial of an SGLT-2 agonist may be appropriate if this has not been previously tried.	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
296	South Sefton CCG	Full	general	general	For improved concordance and macrovascular risk control the pathway needs to be straight forward and should fit on a single page of A4 or equivalent. The NICE version is easier to read but there is as yet no simple algorithm to simplify treatment for primary care teams and the patient. I understand the logic behind the revision but if the concordance rate falls further from the present recorded 30ish percent then the number of complications is likely to increase and as a result the overall cost to the NHS is likely to increase.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm (single A4 page) have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
715	South Tyneside Hospital NHS trust	NICE	12		If standard release metformin is contraindicated or not tolerated consider Repaglinide as the initial drug treatment: If unable to tolerate standard metformin, then modified release should be tried. Long term data shows the overall benefit of metformin	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms.

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						The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
716	South Tyneside Hospital NHS trust	NICE	12		Repaglinide contra-indicated or not preferred patient would need to change to pioglitazone , sulphonylurea or DPP4 before adding another treatment: Although there is a risk of hypoglycaemia with sulphoylureas, we have long term safety data available and generally well tolerated in practice. Side effects like fluid retention and controversies around risk of bladder cancer and fractures exist with Pioglitazone.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
719	South Tyneside Hospital NHS trust	NICE	19 44		Do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless the person is…: Agree with these groups but would like to see an addition for patients with infections eg foot infections.	Thank you for your feedback. The following recommendation has been added: "*Be aware that there is a risk of hyperglycaemia in adults with type 2 diabetes who have acute intercurrent illness. Review treatment as necessary.*"
717	South Tyneside Hospital NHS trust	NICE	General	General	Add pioglitazone to Metformin: Algorithm first intensification: Would prefer Sulphonylurea to be next step, As above re pioglitazone - Controversies around risk of bladder cancer and fractures.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the

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						appropriateness and implementability of these recommendations and associated algorithms. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
718	South Tyneside Hospital NHS trust	NICE	General	General	Add sulphonylurea to above: Algorithm second intensification: Would prefer sulphonylurea to be second stage not 3rd. As above re: pioglitazone.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At second intensification, the guideline development group has recommended the following metformin-based triple therapy options: metformin+pioglitazone+sulfonylurea,

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						metformin+sulfonylurea+DPP-4 inhibitor and in special circumstances metformin+sulfonylurea+GLP-1 mimetic. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
72	Successful Diabetes	NICE	13	1.2.1	It is not enough to offer structured education, the benefits of a programme are in attendance. Good evidence exists for how to offer and how to encourage attendance and these should be included in the guidelines. The reasons for non-attendance are becoming well known and also need to be addressed by 'offerers' in discussion with people they are offering it to. Two recent papers showing what needs to be done are: Winkley, K et al. Patient explanations for non-attendance at structured diabetes education sessions for newly diagnosed Type 2 diabetes: a qualitiative study. Diabetic Medicine, 32, 120-128 (2015). Also, Lawal, M. Barriers to attendance in diabetes education centres: a systematic review. Diabetes and Primary Care, 16, 6, 299-306, 2014	Thank you for your comment. Education was not prioritised within the guideline for update. This decision was taken following a workshop conducted with stakeholders during the scoping of the guideline and stakeholder consultation. It may be possible to address this area in a future iteration of the guideline. This suggestion will be highlighted to the NICE Implementation support team.
73	Successful Diabetes	NICE	19	1.6.5 /	Point 1.6.5 is at odds with 1.6.7 and 1.6.8. If people are to be involved in decisions about their individual targets, it is not then appropriate	Thank you for your feedback. While the guideline development group recognises that there may be circumstances where the recommended targets

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				1.6.7 /1.6. 8	to advise to 'set targets' at a particular level. These targets could be 'recommmended' perhaps, as the start of the discussion with the individual.	are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE version), appropriate aspirational target setting is paramount in ensuring quality patient care.
74	Successful Diabetes	NICE	20/21	1.6.13	The recommendation to 'do not offer' is inconsistent with a patient centred approach as SMBG is the only tool which people have available that can give them any sort of control over their day to day decisions and learn the effect of lifestyle changes that are so keenly recommended, and as such, they may choose that it will be beneficial to them.	Thank you for your feedback. The guideline development group does not agree that a recommendation that does not promote the routine use of self-monitoring of blood glucose (SMBG) shown to be ineffective in improving HbA1c levels is inconsistent with quality patient centred care. The guideline development group has identified clinical circumstances when SMBG is useful and has included these in the recommendation.
75	Successful Diabetes	NICE	20/21	1.6.13	If repaglinide is to be used at first line therapy after Metformin, as an insulin secretagogue, this will definitely put a person at risk of hypoglycaemia and therefore should be included as an indication for offering SMBG, so they can keep themselves safe from this side effect	The guideline development group looked at the best available evidence on self-monitoring in people with type 2 diabetes. Their conclusion based on this evidence and taking into account clinical experience and patient concerns was that routine self-monitoring of blood glucose should not be recommended. However, the guideline development group has identified clinical circumstances when self-monitoring of blood glucose is useful, as described in your comment and has included these in the recommendation.
76	Successful Diabetes	NICE +Full	22	1.6.19	Repaglinide is a short acting drug, requiring multiple doses. Multiple doses means increased chance of forgetting to take one or more per day. Explaining this fact to people, as well as explaining about changing to pio if it is insufficient, should be included in the guidance,	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these

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					It is not enough to expect clinicians to read the guidance on medication adherence. People taking the tablets themselves need to know and work out how to overcome the difficulties multiple doses present. The full guidance explains that the GDG were aware of the multiple dose issue with repaglinide in making their decision. Did they also take into consideration that adding repaglinide makes the multiple dose issue apply now to both metformin and repaglinide?, At one stroke, doubling the daily burden of medication taking. This will inevitably lead to more, not less, issues of missing medication, which will not be helpful in achieving the targets for blood glucose.	recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, recommendations referring to repaglinide make clear in footnotes that "Repaglinide has a marketing authorisation for use only as monotherapy or in combination with metformin. Therefore, for people who cannot take metformin, there is no licensed combination containing repaglinide that can be offered at first intensification. Patients should be made aware of this when initial therapy is being discussed" and to "Be aware that initial drug treatment with repaglinide should be stopped and the drugs in the dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug." This information is also reflected in the algorithm. A generic recommendation has also been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest

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						acquisition cost).
68	Successful Diabetes	NICE +Full	General	General	There is very little mention of the emotional impact of living with diabetes. Nor is any mention made of formal psychological or psychiatric assessment, support and referrals that may be needed, especially with the burden of depression and anxiety experienced in long term conditions, and particularly type 2 diabetes. Evidence 1-6 below shows that this is important and can be practically implemented to good effect and impact. Other evidence is available. May I suggest that this aspect, or a reason for its omission, is acknowledged in the guidelines, as currently this is a major omission of a body of relevant and important evidence. It is insufficient to cite other NICE guidance eg Depression in Adults and in long term conditions, in the end matter of the guidelines without referring to it in the body of the guidance. Please note that much of the guidance on emotional and psychological support for young people with Type 2 diabetes in the CYP guideline consultation could equally apply to adults with Type 2 diabetes.	Thank you for your feedback. It was not within the scope of the guideline to consider formal psychological support or psychiatric assessment for people with type 2 diabetes. However, NICE recognises that the emotional impact of living with diabetes is an important issue. The NICE pathway on diabetes will link to recommendations on depression in adults with a chronic physical health problem and also the NICE guidance on patient experience in adult NHS services.
69	Successful Diabetes	NICE +Full	General	General	1. Dietrich U. Factors affecting the attitudes held by women with Type 2 diabetes: a qualitiative study. Patient educ couns 1996 29(2) 13-23 2. Polonsky, W et al. Are patients' initial	Thank you for these references.

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					experiences at diagnosis, associated with attitudes and self-management over time? Diabetes Educ 2010 36 (5) 828-34 3.Levinson, W. et al. A study of patient clues and physician responses in primary care and surgical settings' JAMA, 2000, 284, 1021-1027 4. 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 psychsological well-being in people with diabetes. Diabetic Med, 32, 155-163 (2015) 5. Nash, J. Dealing with diagnosis of diabetes. Practical Diabetes, 32, 1, 19-23 6. Williams et al; supporting autonomy to motivate patients with diabetes for glucose control. Diabetes Care, 21, 10, 1644-1651 1998	
71	Successful Diabetes	NICE +Full	General	General	Recent evidence has highlighted the particular needs of young adults with type 2 diabetes, a growing group. Should this be addressed in the updated guidance, particularly as it is unlikely to be updated soon and this group of people is likely to grow exponentially? Paper below: Browne, JL et al. Depression, anxiety and self-care behaviours of young adults with Type 2 diabetes: results from the International Diabetes Management and Impact for Long Term Empowerment and Success (MILES) study. Diabetic Medicine, 32, 133-40 (2015). A related paper reveals further information about adolescents with Type 2 diabetes which may be	Thank you for your feedback. The diagnosis and treatment of children with type 2 diabetes has been covered by the Diabetes in Children and Young People guideline which is being updated at the same time as this guideline on type 2 diabetes in adults.

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					worthy of note in the guidance, as older and frail people are already mentioned. Alternatively, include in the CYP guidance on Type 2 diabetes and cross reference in this guidance. Paper below: Turner, KM et al. Adolescents' views and experiences of treatments for Type 2 diabetes: a qualitiative study. Diabetic Medicine, 32, 250-256 (2015)	
70	Successful Diabetes	Full NICE	General	General	There appears to be no mention of an annual review of clinical and psychological aspects of Type 2 diabetes.	Thank you for your feedback. It was not within the scope of the guideline to consider the components of diabetes annual review. However, the guideline includes a generic recommendation "*Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective.*" It is anticipated that healthcare professionals would consider both the clinical and psychological circumstances of the person with type 2 diabetes throughout ongoing care.
570	SurreyDowns CCG	Full	11	33	Our comments are that these points make good sense and that it is beneficial to encourage	Thank you for your feedback.

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				-36	adults with type 2 diabetes to be involved in decisions about their HbA1c targets	
571	SurreyDowns CCG	Full	13 to 15	General	Algorithm for blood glucose lowering therapy – The algorithms which should assist in the sequencing of drugs are confusing and complicated. The algorithm does not make the place in therapy of the newer agents such as the SGLT2 inhibitors clear. It should also include a recommendation of using the MR preparation of metformin for patients intolerant to the standard release. Instead it suggests the use of alternative agents all of which can cause weight gain, some that can cause hypoglycaemia and others with MHRA safety concerns. The GDG noted that their clinical experience suggests that repaglinide is associated with the largest reduction in HbA1c but the highest number of hypoglycaemic events and also weight gain. We feel it is important that this information is noted within the algorithms. The group had already decided to note the licensing limitations to make people aware of this particular constraint. We feel that the limitations of weight gain and hypoglycaemia are also important constraints for patients to consider which underlines the importance of safety considerations to be included in the algorithms Intensification only at HbA1c > 58mmol/mol is not fully explained within the algorithm. Information on starting a GLP1 mimetic is sparse and more information within the	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The algorithms have been simplified to a single A4 page and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The algorithm reflects the recommendations and includes: - the recommended use of metformin modified-release in circumstances where standard-release metformin is not tolerated - cross-referral to NICE technology appraisal guidances on SGLT-2 inhibitors where appropriate - a footnote on MHRA guidance on safety alerts

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					algorithm would be helpful We feel it would have been more ideal to have included the safety concerns of each agent included within the table. This would assist the prescriber with shared decision making. In our experience algorithms are often used in isolation from the original documents so this presents an additional concern.	for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug - guidance on setting HbA1c targets - starting and stopping rules for GLP1 mimetics.
572	SurreyDowns CCG	Full	16 to 17	General	The guidance on patient education, lifestyle modification, monitoring and targets are logical and allow for flexibility of structured education programmes, all of which are achievable in the primary care setting. We agree that there is little evidence to support one particular educational programme over another.	Thank you for your feedback.
576	SurreyDowns CCG	Full	173	Feneral	Section 8.4.3 health economic considerations. We are concerned that the health economic modelling used does not sufficiently account for the benefits of weight loss and potential harms of hypoglycaemia of blood glucose lowering treatment. How the weightings are assigned in health economic modelling for the different harms and benefits of blood glucose lowering treatments would significantly impact on proposed drug choices, and we think the current model has too many limitations in this respect.	Thank you for your feedback. The guideline development group considered that the costs and utilities assigned to weight change (gain and loss) and hypoglycaemic episodes were adequate. Cost and QALY results were presented disaggregated to explore the impacts of long-term complications, drug costs, weight changes and, dropouts and hypoglycaemic epsiodes. Sensitivity analyses (reported fully in appendix F) explored the impacts of alternative weightings and assumptions regarding utilities associated with weight changes and hypoglycaemic episodes.
57	SurreyDo	Full	19	Gen	Recommendations 38 – 41 - We believe that the	Thank you for your feedback. The guideline

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3	wns CCG			eral	sensible target of 53mmol/mol when drugs that can cause hypoglycaemia are introduced is practical in the primary care setting. However we are concerned that waiting until the patient has an HbA1c of 58 mmol/mol before adding in initial drug treatment and then having a target of 53 mmol/mol is potentially a backward step for that group of patients when many of them are patients with low risk of hypos, adverse affects, long life expectancies, absent, co-morbidities and absent vascular complications who are highly motivated, with resource available who may benefit from more stringent management of their hyperglycaemia as it approaches 57mmol/mol. What appears confusing is that there then seems to be 3 targets: 48mmol/mol for patients to have one drug or just lifestyle and diet waiting until > 58mmol/mol when you add in a second drug but then aiming for a target level of 53mmol/mol for those patients on 2 drugs That suggests an overlap between 49mmol/mol and 57mmol/mol where patients could not be treated with a second drug or a patient between 53 and 57mmol/l that is. We think that the advice on balancing benefit of glycaemic control against harms could be more effectively illustrated. For example using the model used in the recent ADA-EASD guidelines	development group purposely did not select a drug intensification threshold of 53 mmol/mol (7%) with an associated HbA1c target of 48 mmol/mol (6.5%) as it was considered too low and inappropriate for most people as the condition progresses. In addition, the group considered the natural fluctuating error observed in HbA1c measurements of about 2 mmol/mol (0.2%). There are 2 recommended HbA1c targets: 1) 48 mmol/mol (6.5%) for people managed on diet/lifestyle or in combination with a single drug not associated with hypoglycaemia (see Recommendation 1.6.7 in NICE version). This group of individuals would typically fall in the category of those early in the disease process. However, due to the variable trajectory of diabetes, the guideline development group did not think it would be accurate to specify only this subgroup. 2) 53 mmol/mol (7%) for people who require drug intensification (see Recommendation 1.6.8 in NICE version). 58 mmol/mol (7.5%) is not a target but a threshold for intensifying drug treatment. This suggestion of decision aids to inform selection of blood glucose targets will be passed on to the NICE implementation team.

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					[1] may be a more useful for approach for primary care practitioners to use when assessing their approach for the management of hyperglycemia in their patient population. Linked to this point, we would like to see consideration of which patient groups may benefit from tighter blood glucose control e.g. younger newly diagnosed type 2 diabetic, as well as the proposed more relaxed target for some specified patient groups. [1] Inzucchi SE, Berganstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140-9. http://dx.doi.org/10.2337/dc14-2441	
577	SurreyDowns CCG	Full	196	12 -14	Although both rapliginide and sulphonylureas are cost-effective, they have been associated with higher rates of hypoglycemia which suggests caution will be required in specific populations eg.frail elderly which should be made clearer to the precribing physician.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and

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						emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
578	SurreyDowns CCG	Full	196	27	Our comments are that there is evidence to suggest that both sulponylureas and pioglitazone can increase weight that may be unacceptable for many patients. The guideline should include a recommendation about how this information is made clear to patients.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to discuss the benefits and risks of drug treatment, and the options available with the individual; and to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).

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575	SurreyDowns CCG	Full	20	33	The choice of repaglinide as a first line alternative for patients that cannot tolerate metformin is unexpected. Repaglinide has a complex escalating dosage regimen at initiation with the potential to be a three times a day medication (thus raising concerns around adherence) with the additional complexity of a limited license. The recommendation appears to have been made despite the wide confidence intervals for HbA1c lowering for repaglinide treatment as initial blood glucose lowering therapy. It is an unfamiliar drug in the armoury of many primary care physicians (hence raising an educational need), which will be problematic with respect to implementation of this recommendation. Additionally, clinicians will need to be aware of the potential drug interactions that can occur eg. Trimethoprim. For patients intolerant to metformin it is likely to be confusing for patients to start repglinide and if not effective then change both this drug and add in a second agent at the same time suggesting the potential for both prescribing and adherence errors and complex consultations.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
574	SurreyDowns CCG	Full	20	General	We generally support the guidance on self-monitoring of blood glucose.	Thank you for your feedback.
579	SurreyDowns CCG	Full	271	31	Reference should be made to the MHRA safety advice issued in May 2014 regarding the cardiac side effects of domperidone and the MHRA safety advice issued in May 2013 regarding the neurological adverse effects of metoclopramide.	Thank you for your feedback. This section of the type 2 diabetes guideline was not prioritised for update following a stakeholder workshop and stakeholder consultation at the scoping stage. It was considered by the type 1 diabetes guideline

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					Signposting to the NICE ESUOM on oral erythromycin would be useful here.	and both guideline development committees agreed that the management of gastroparesis was likely to be similar between people with type 1 and type 2 diabetes. Therefore, 2 recommendations on the treatment of gastroparesis from the type 1 diabetes guideline have been adopted in the type 2 diabetes guideline. In the recommendations, domperidone is recognised as having the strongest evidence for effectiveness but that it should only be used in exceptional circumstances when metoclopramide or erythromycin have not been effective, based on the recent safety issues highlighted by the MHRA.
568	SurreyDowns CCG	Full	General	General	The specific recommendations detailed are clear. However, our concern is the length of the document and the time required for clinicians to fully understand all the recommendations. There will be an educational issue and we would welcome the development of suitable summarised implementation tools .	Thank you for your feedback. The suggestion will be passed to the implementation team.
569	SurreyDowns CCG	Full	General	General	Choice of blood glucose lowering agents – we have some concerns that the choice of blood glucose lowering treatment in the guideline – particularly with respect to pioglitazone, and sulphonylureas, has been made without reference to the wider literature on the safety concerns about these agents. For example pioglitazone – MHRA warnings about risk of heart failure, bladder cancer, and also concerns	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-

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					about fractures and pneumonia; and the more recent increasing concerns regarding cardiovascular safety of sulphonylureas. In addition the DVLA recommendations on blood glucose monitoring for sulphonylureas do not appear to have been included in modelling. The place of the SGLT2 inhibitors is vague and requires clinicians to be familiar with other NICE guidance. It is unclear how a clinician should include a SGLT-2 inhibitor at second intensification – more information would be useful Although the guidance suggests introducing the new medicines in a stepwise manner checking tolerability of each this may not be easy to achieve practically as repeated consultations will be needed and patients may be unable to attend many frequent appointments. Emphasis on safety concern rather than just tolerance would also be useful Primary care clinicians will find the drug treatment choices in the guideline confusing and difficult to implement when trying to balance safety, adherence, tolerability and effectiveness in such a hard to treat group of patients	release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Recommendation 1.6.12 (NICE version) states "*Take the Driver and Vehicle Licensing Agency (DVLA) At a glance guide to the current medical standards of fitness to drive into account when offering self-monitoring of blood glucose levels for adults with type 2 diabetes.*" In addition, recommendation 1.6.13 (NICE version) notes

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						that self-monitoring of blood glucose should be undertaken for adults with type 2 diabetes who are "*on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery*". Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
890	Swansea NHS Trust	Full	12	19	The recommendation for repaglinide as the first-line therapy for people with T2DM in whom metformin is inappropriate, or not tolerated, is odd. In ABMU Health Board, this agent is rarely prescribed, even by General Practitioners with an active interest in T2DM. To reinforce this comment, our pharmacy system across the five acute sites (a catchment population of ~500,000) has only dispensed only 4 packs of repaglinide over the last 18 months	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated.
89	Swansea	Full	12	19	In an era where all new T2DM medicines require	Thank you for your feedback. The guideline

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1	NHS Trust				the back-up of a cardiovascular outcomes trial (CVOT), repaglinide has only modest clinical trial support and it is a thrice-daily agent which (according to license, and acknowledged by this draft) can only be used as a combination regimen with metformin. So, at the point of therapy escalation, it would have to be with-held. 'Treatment inertia' in the management of T2DM is rife throughout UK practice and is likely to be worsened by this draft which recommends (P21,L25) "when switching from repaglinide to any of these combinations, introduce the 2 new medicines in a stepwise manner, checking for tolerability of each"; so, patients with sub-optimal glycaemic control move from monotherapy with one agent to monotherapy with another….	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
892	Swansea NHS Trust	Full	12	19	One is led to surmise that the CG group are acknowledging the safety issues of hypoglycaemia, weight gain and, perhaps cardiovascular (CV) risk, with sulphonylureas (the previous first-line alternatives from CG87) but opting to replace these with a less-well researched alternative. Not even cost can be a an argument since gliclazide, a medication with which there is much more familiarity in Wales, is much cheaper.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
893	Swansea NHS Trust	Full	14	Figure 2	The elevation of pioglitazone from third-line option in CG87 to default second-line after metformin (and alternative first-line therapy) is	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the

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					also strange. When CG87 was published in 2009, the positive CV data for pioglitazone from the PROACTIVE study had already been in the scientific (and public) arena for four years. Since that time, almost all of the 'theme-music' around thiazolidinediones (TZDs) has been negative: rosiglitazone was banned from use in Europe because of concerns that it might increase CV risk; pioglitazone was banned from use in France because of concerns that it might increase the risk of bladder cancer (a signal for which had been seen in phase 2 clinical trials); and the TZD class side-effects such as bony fracture and volume overload had been confirmed in several clinical trials. So, the only thing that seems to have changed in favour of pioglitazone is that it has come off patent and is now much cheaper than before.	pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm.
894	Swansea NHS Trust	Full	14	Figure 2	Whilst we did not buy-in to the CV risk story for rosiglitazone (this was subsequently withdrawn by the FDA), nor the pioglitazone bladder scare (not supported by the most recent Kaiser Permanente prospective data), there is no doubt that primary care prescribing of pioglitazone has plummeted over the past four years. This trend has been supported by local pharmacy advisors who, one might imagine, would be less then keen to reverse their position so as to conform with this latest NICE draft.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. A footnote on MHRA guidance on safety alerts for pioglitazone

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						and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has also been added to the recommendations and algorithm.
895	Swansea NHS Trust	Full	14	Figure 2	The minimal referral to SGLT-2 inhibitors in the draft, on the basis that they have been assessed by individual technology appraisals (TAs) by NICE, is problematic. This class of oral anti-diabetic drug has now been available for use in the EU since 2012 and should clearly be included in any new recommendations. This has echoes of the NICE CG66, published in 2008, which immediately accepted that it's glycaemic control section was out-of-date (hence CG87, published almost exactly one year later); how can a similar outcome be justified?	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
896	Swansea NHS Trust	Full	15	Figure 3	The guidance relating to DDP-4 inhibitor choice is interesting in that it consistently recommends the 'option with the lowest acquisition cost'. In Wales, following assessment by the All-Wales Medicines Strategy Group (AWMSG), named DDP-4 inhibitors have been approved for specific uses and these do not allow for use of the cheapest agent for all indications. Does this NICE draft seek to override that guidance?	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
899	Swansea NHS Trust	Full	18	22	**Blood pressure management** The management of blood pressure (BP) in this NICE draft is essentially unchanged from that of CG87. As such, it is out-of-step with the latest guidance from the eight joint national committee	Thank you for your feedback. Blood pressure therapy was not prioritised for update within this iteration of the type 2 diabetes guideline following a stakeholder workshop and stakeholder consultation conducted at the

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					(JNC 8) in the United States (2014), which has relaxed the BP targets to 140/90 mmHg.	scoping stage. As no new evidence review had been undertaken, it is not possible to make changes to the recommendations. Therefore recommendations on hypertension from the previous iteration of the type 2 diabetes guideline have been retained.
900	Swansea NHS Trust	Full	19		Whilst one can debate the actual targets in this area, we feel that, once again, NICE is missing out on the opportunity to promote individualised goals. Although an 'individually agreed target' is mentioned in the context of anti-hypertensive triple therapy (P18, L19), this is not emphasised and the potential for harm from drug-induced hypotension, especially in the elderly T2DM patient is ignored. A specific recommendation to measure sitting and standing BP would go some way to addressing this issue and should, in our opinion, be included in the current draft guidance.	Thank you for your feedback. The guideline development group agrees that HbA1c targets of 48 or 53 mmol/mol (6.5 or 7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Blood pressure therapy was not prioritised for update within this iteration of the type 2 diabetes guideline following a stakeholder workshop and stakeholder consultation at the scoping stage. Therefore it is not possible to make changes to recommendations around blood pressure management.
898	Swansea NHS Trust	Full	20	42	Finally, let us focus on the glycaemic scenario where (P20,L42 onwards) "if both standard-release metformin and pioglitazone are contraindicated or not tolerated, and repaglinide is contraindicated, not tolerated or not preferred" consideration is given to..... initial drug treatment with a sulphonylurea. This is such an unlikely clinical suggestion that it should never be included in a guideline!	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased

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						emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
897	Swansea NHS Trust	Full	22	37	The requirement for GLP-1 mimetic therapy to have both a reduction of 1% (11mmol/mol) HbA1c reduction AND a weight loss of 3% initial body weight in the first six months of treatment does not recognize that larger decrements of either parameter might occur in isolation and can be of important clinical benefit. An either/or 'stopping rule', as has already been adopted by our Health Board, is more appropriate in our view.	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. GLP-1 mimetics appear in the algorithm and are only recommended in specific circumstances.
895	Swansea NHS Trust	Full	General	General	We welcome the review of the NICE Clinical Guideline (CG) 87 for type 2 diabetes (T2DM) and support many of the recommendations that are made.	Thank you for your feedback.
896	Swansea NHS Trust	Full	General	General	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 and where we would suggest revision (sometimes radical revision) should be made.	Thank you for your feedback.
897	Swansea NHS Trust	Full	General	General	**Blood glucose management** Although the draft CG update mentions 'individual HbA1c' targets (e.g. Page (P) 11;Line (L) 33, P19;L6 & P19;23-36) the algorithms, which (if anything) are most likely to be used	Thank you for your feedback. Along with all other stakeholder feedback, the blood glucose management algorithm has been modified.

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					from this document, have a major focus on the threshold HbA1c of 7.5% (58mmol/mol) and target of 7.0% (53mmol/mol). To illustrate, 7.5% (58mmol/mol) is detailed twenty-six times in figures 1-3 (pharmacological treatment algorithms for initiation, first and second intensification of therapy, P13-15).	
898	Swansea NHS Trust	Full	General	General	**Blood glucose management** The recommendations are generally far too specific and prescriptive, and at odds with the EASD/ADA consensus view that glycaemic management in general (not just HbA1c targets) should be individualised. One could argue that doctors and nurses who need the super-specific guidance detailed in this draft should not be undertaking the management of this complex condition; indeed, they are unlikely to have ever heard of one of the first-line treatment recommendations (repaglinide), let alone to have prescribed it.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
901	Swansea NHS Trust	Full	General	General	**Lipid management** Lipid management in T2DM is entirely deferred to the NICE CG181 (2014) and whilst this is	Thank you for your comment. The section on lipid management which existed in the previous iteration of the type 2 diabetes guideline has

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					positive in terms of consistency, there are some issues that will still need to be resolved: · The use of the QRISK2 risk assessment tool to assess cardiovascular (CVD) risk in people with T2DM introduces an extra layer of complexity, rather than the previous cut-off of 40 years from CG66. · 'Non-HDL cholesterol' is a completely new concept for most clinicians working in the field of diabetes and is not reported by Clinical Chemistry laboratories in Wales. There needs to be a period for education and a change-over in reporting before this can be adopted. · The suggestion that the 'target' for lipid management should be a 40% reduction in non-HDL cholesterol means that practice audit of lipid-lowering in T2DM will become almost impossible. Non-HDL cholesterol will not have been documented previously; the starting level of non-HDL cholesterol is unlikely to have been recorded; is it the starting level of non-HDL cholesterol or that achieved on a previous statin regime?	been updated by the publication of Lipid modification (CG181) in 2014. It is not possible to look further into these areas which will have been consulted on prior to the publication of CG181.
90	Swansea	Full	Gene	Gen	Whilst CG181 (appropriately) excludes the	The section on lipid management which existed

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2	NHS Trust		ral	eral	routine use of fibrates and other lipid-lowering agents for use in T2DM, it was published before the positive CV data for ezetimibe. This guideline should be able to give advice, especially for people with T2DM and established CV disease, where ezetimibe is often denied on the basis of cost (and the previous lack of CV outcome data) but in whom it may be an appropriate intervention.	in the previous iteration of the type 2 diabetes guideline has been updated by the publication of Lipid modification (CG181) in 2014. It is not possible to look further into these areas which will have been consulted on prior to the publication of CG181.
698	TAKEDA UK Ltd	Full	176	6	The original health economic modelling undertaken by NICE for this guideline did not take into account the need for some treatments to have self monitoring of blood glucose (SMBG) for patients. As the draft recommendations for agents that can cause hypoglycaemia, such as repaglinide, warrant SMBG (see recommendations 1.6.12 and 1.6.13) we suggest that further sensitivity analyses are conducted to see if this impacts on the favourable positioning of repaglinide that resulted from the current analyses.	Thank you for your feedback. Self-monitoring of blood glucose (SMBG) costs were included in the original health economic modelling as part of "drug resource use". Full details can be found in appendix F (3.9). Thank you for this comment, which calls for further analysis. It was considered alongside all other comments on review question 1 that called for further analysis. The view of NICE and the guideline development group was that, on this occasion, any such further analysis would be of limited assistance to the Group. Accordingly, the revision of the section on pharmacological management of blood glucose levels has been based on a revised interpretation of the evidence available from the existing clinical reviews and health economic modelling in the light of what stakeholders have said. Please see the Linking Evidence to Recommendations tables in sections 8.4.11, 8.4.15 and 8.4.18 for details of the reasoning behind the final recommendations.

Type 2 diabetes (update)

Consultation on draft guideline - 07/01/15 to 05/03/15
Stakeholder comments table with responses

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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697	TAKEDA UK Ltd	Full	20 13	33 -38 Figure 1	The prominent positioning of repaglinide is not reflective of clinical practice in the UK. Although being available for a considerable number of years, in the 12 months leading to December 2014, only 0.2% of patients with Type 2 diabetes were prescribed repaglinide. [Dec 2014, CSD patient data; report 1]. We suggest that it is made clear that repaglinide is **only** to be considered as an option for patients unable to take metformin as an alternative alongside rather than in preference to other options (such as a DPP-4 inhibitor, pioglitazone or an SU). It is also important that further guidance is added and the importance increased for selection criteria in identifying suitable patients for treatment, such as for patients to agree to its use after being well informed of the risks of hypoglycaemia and that when they progress further with this chronic disease, they will have to change to differing treatments. Realistically, it is likely that only a very small cohort of patients will fall into this category and benefit from repaglinide treatment. This is not ideally portrayed in the algorithms and recommendations for this draft guideline as on first sight undue prominence to this older	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. In addition, recommendations referring to repaglinide make clear in footnotes that "Repaglinide has a marketing authorisation for use only as monotherapy or in combination with metformin. Therefore, for people who cannot take metformin, there is no licensed combination containing repaglinide that can be offered at first intensification. Patients should be made aware of this when initial therapy is being discussed" and to "Be aware that initial drug treatment with repaglinide should be stopped and the drugs in the dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug." This information is also reflected in the algorithm. A generic recommendation has also been added and emphasised in the algorithm to base choice of

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					therapy that is not currently widely used in clinical practice (i.e. repaglinide) may be misinterpreted for use in a wider cohort of patients than would be ideal and this could ultimately jeopardise patient care.	drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
694	TAKEDA UK Ltd	Full	20 21 22	42-46 1-3 12-15 16-24 28-35 40-43 1-11	Takeda UK Ltd are pleased that, following a review of the DPP-4 inhibitor evidence base, the GDG concluded that DPP-4 inhibitors should be recommended as a class, with a recommendation that the final choice of individual agent should be that with the lowest acquisition cost available to the prescriber. We agree that, for the most, there seem to be more similarities than differences between the DPP-4 inhibitors. This is not only supported by NICE's own meta-analyses / network analyses, but also other independent meta-analyses[15-18] and by the ADA/EASD joint guideline.[19] Most recently, Craddy et al. showed that comparisons between the DPP-4 inhibitors, alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin, as monotherapy and as dual therapy with metformin, demonstrated non-inferiority for key efficacy and safety outcomes (HbA1c change from baseline, patients achieving HbA1c <7%, change in weight from baseline and patients with hypoglycaemic events) in patients	Thank you for your feedback.

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					with uncontrolled Type 2 diabetes mellitus.[18] There is only one published head to head study comparing one DPP-4 inhibitor against another; in this 18 week study, Sheen et al. saxagliptin plus metformin was noninferior to sitagliptin plus metformin, and was generally well tolerated.[22] Although there are slight differences between some of the indication wording between the DPP-4 inhibitors, for the most part, there are more similarities than differences for those areas in which they are most widely used and recommended (i.e. dual therapy and triple therapy and as add on to metformin and/or a sulphonylurea).[23]	
695	TAKEDA UK Ltd	Full	21	4 -15 16-27 28-35 40-43	Recommendation 1.6.22 DPP4i in first intensification of therapy (dual therapy) The recommendations for use of a DPP-4 inhibitor are inconsistent between the 'initial therapy' and 'first intensification of therapy' stages. At initial therapy, if repaglinide is contra-indicated or not preferred, and if pioglitazone is contra-indicated, **a DPP-4 inhibitor or a sulfonylurea are recommended based on patient preference following a discussion of benefits and harms.**	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor.

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					However, at first intensification of therapy for uncontrolled patients (HbA1c ≥ 58mmol/mol or 7.5%) already on metformin, the group suggest to add in pioglitazone unless contra-indicated, in which case to add in a sulfonylurea. **If a sulfonylurea is contraindicated too or not tolerated then a DPP-4 inhibitor can be added to metformin.** We recommend this is corrected to state at first intensification of therapy to choose between a DPP-4 inhibitor and a sulphonylurea **based on patient preference following a discussion of benefits and harms.**	
692	TAKEDA UK Ltd	Full / NICE	General	General	Takeda UK Ltd. welcome an update to the NICE guideline on the management of Type 2 diabetes. Since the publication of CG87 in 2009, a number of newer therapies and data have become available as well as therapies coming off patent, and thus a review and update of the guidelines are timely and appropriate. We appreciate that the scope of the guideline is broad and there has been a significant amount of information and data to consider and analyse when producing the draft. In general, Takeda support some of the main recommendations of the guideline. Takeda UK Ltd are pleased that the guidelines provide a variety of options to the prescriber for patients	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs,

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					with uncontrolled hyperglycaemia. Importantly the timing and choice of treatment is based on the individual, whether this is determining the HbA1c target or the agent(s) to be used. However, we feel in places the draft wording for recommendations and the draft algorithm do not make this clear to the reader. In addition, we would welcome a more comprehensive review of the available evidence.	available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
693	TAKEDA UK Ltd	Full NICE	General	General	It was clear from the Scoping document (published in November 2012) that only medicines available in the UK prior to December 2012 would be included with an initial publication date of the guideline as June 2014. However, since this time Takeda UK Ltd have launched the DPP-4 inhibitor alogliptin in the UK (January 2014) and the guideline publication has been delayed until August 2015. We are pleased that the Guidelines Development Group did include alogliptin within their search strategies to identify data even if the data for alogliptin were not fully assessed within the evidence review. As alogliptin has been available in the UK since January 2014, with the majority of data published before this date, we would welcome a fuller review of the data, including the wealth of	Thank you for the feedback. The recommendations in the guideline are based on the clinical effectiveness review and health economic modelling analysis of available evidence identified by a cut off search date of June 2014. Any studies published after this date could not be included in this update. Studies including alogliptin were identified in the searches but were excluded as comparisons were across treatment strategies (see Appendix L rows 588 and 761).

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					alogliptin evidence that has since published, and also outcomes studies in diabetes that have reported in recent years, such as the alogliptin EXAMINE study. However, we understand the time constraints and subsequent delay this would pose to guideline publication. Since alogliptin was first launched in Japan in 2010, there have been 1,619,770 cumulative patient years exposure.[1] Alogliptin has been studied extensively in patients with a variety of disease complications, including older patients (aged ≥65 to 80 years) and patients at very high risk of CV events. Currently, there are over 150 publications relating to alogliptin, of which nine are key phase 3 clinical trials for alogliptin alone or in combination with metformin.[2-10] The alogliptin clinical trial programme investigated the efficacy and safety of alogliptin as add-on to a range of therapies in approx. 14,800 patients including elderly and renally impaired patients when compared with placebo and active comparators.[11] A summary of evidence and recommendations for alogliptin are detailed below. **Indications**	

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					Alogliptin is indicated in adults aged 18 years and older with T2DM to improve glycaemic control in combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Therefore alogliptin is not licensed for use in monotherapy, but **can be used in combination with other therapies, e.g. in dual therapy, triple therapy, or with insulin.** **Efficacy** • Alogliptin improves glycaemic control in combination with other glucose-lowering treatments for adults with T2DM[2-6] • At 26 weeks, alogliptin is associated with an average reduction in HbA1c of between 0.5-0.9% (5.5-9.8 mmol/mol) from baseline when added to metformin, an SU, pioglitazone or insulin[2-6] • When added to metformin, alogliptin demonstrated a durable reduction in HbA1c levels that was statistically superior to a sulphonylurea plus metformin (glipizide) at 2 years (mean dose 5.2 mg)[7] • Alogliptin provides similar HbA1c reductions in older (≥65 years) and younger patients (<65 years) with no differences seen in the safety profile[12]	

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					Hypoglycaemia • Across 12 studies, the overall incidence of hypoglycaemia was lower in patients treated with alogliptin than in patients treated with active control or placebo[11] • Alogliptin was not associated with an increased incidence of hypoglycaemia, even when added to an SU[4] • In a pooled analysis, there was no apparent difference in the incidence of hypoglycaemia between patients aged ≥65 years and patients <65 years[9]* **Effect on weight** • Alogliptin has generally neutral effects on body weight[11] **Cardiovascular (CV) safety** • The CV safety of alogliptin was evaluated in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study, a multicentre, randomised, double-blind, phase 3 trial of very high risk patients with T2DM who had experienced an ACS event 15-90 days prior to randomisation[13] • Alogliptin plus standard-of-care achieved its primary endpoint and did not increase the incidence of major adverse CV events compared with placebo plus standard-of-care in patients with uncontrolled T2DM at high risk of	

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					CV events[13] – Alogliptin plus standard-of-care did not increase the incidence of CV death (HR 0.79; 95% CI 0.60-1.04), non-fatal myocardial infarction (HR 1.08; 95% CI 0.88-1.33) or non-fatal stroke (HR 0.91; 95% CI 0.55-1.50)[13] • Hospitalisation for heart failure occurred in 3.1% of patients on alogliptin versus 2.9% on placebo (HR 1.07, 95% CI 0.79 -1.46), demonstrating no increased risk of heart failure in a *post hoc* analysis of the EXAMINE study[14] • When added to standard-of-care therapy, alogliptin resulted in significantly greater reductions in HbA1c with no increase in hypoglycaemia compared with standard-of-care plus placebo[13] • When added to standard-of-care treatment, alogliptin was well tolerated in this very high risk population, there was no significant difference between adverse events (AEs), reported malignancies, renal function, pancreatitis and risk of hypoglycaemia between alogliptin and placebo[13] **Drug to drug interactions[12]** • Alogliptin demonstrates negligible metabolism by the cytochrome (CYP) 450 enzyme system, without p-glycoprotein inhibitor or substrate interactions, so there is a low potential for drug-drug interactions	

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					Dosage and administration[12] • Once daily dosing • Alogliptin has approved doses for all stages of renal impairment and is available in tablet strengths appropriate for the different stages of renal impairment - Mild renal impairment – no dose adjustment necessary - Moderate renal impairment – 12.5 mg once daily - Severe renal impairment or ESRD – 6.25 mg once daily **Contraindications**[12] • Alogliptin is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients; or with a history of a serious hypersensitivity reaction (including anaphylactic reaction, anaphylactic shock, and angioedema) to any DPP-4 inhibitor **Key Precautions** • Alogliptin is not recommended in patients with severe hepatic impairment (Child-Pugh score >9) as it has not been studied in this group. • Patients should be observed closely for possible liver abnormalities. Post-marketing reports of hepatic dysfunction including hepatic failure have been received with alogliptin, although	

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					a causal relationship has not been established. In patients with symptoms suggestive of liver injury, liver function tests should be obtained promptly and if an abnormality is found and an alternative aetiology is not established, discontinuation of alogliptin should be considered. • As there is a need for dose adjustment in patients with moderate/severe renal impairment and ESRD requiring dialysis, appropriate assessment of renal function is recommended prior to initiation of therapy and periodically thereafter. Experience in patients requiring dialysis is limited. Alogliptin has not been studied in patients undergoing peritoneal dialysis. • Alogliptin is not recommended in patients with congestive heart failure of NYHA functional class III and IV since there is limited experience of alogliptin use in clinical trials in these patients. • Caution should be exercised in patients with a history of pancreatitis as the use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, alogliptin should be discontinued; if acute pancreatitis is confirmed, alogliptin should not be restarted.	

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					• Due to the increased risk of hypoglycaemia in combination with an SU, insulin or combination therapy with TZD plus metformin, a lower dose of these medications may be considered to reduce the risk of hypoglycaemia when these medicinal products are used in combination. **Cost** •The basic NHS list price of alogliptin (£26.60 for 28 days treatment) and provides up to a 20% saving vs. other DPP-4 inhibitors. Prescriptions to manage diabetes in primary care cost the NHS £2.2 million on average every day in 2013-14. Almost 10 per cent (9.5 per cent) of the total primary care drugs bill was spent on managing diabetes and this shows a continuous annual rise from 6.6 per cent in 2005-06.[20] The NHS spend on DPP-4 inhibitors was £125.2 million in the year preceding October 2014, which was a 20% growth compared to the previous year.[21]	
696	TAKEDA UK Ltd	Full	General	General	Takeda UK Ltd acknowledges the inclusion of pioglitazone in the treatment armamentarium as an option for appropriate patients. Takeda is confident in the therapeutic benefits of pioglitazone and its importance as a treatment for T2DM, when used in a manner consistent with the product prescribing information.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A

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					Initiation of pioglitazone therapy should be in line with the recommendations in the latest Summary of Product Characteristics (SmPC). However, we believe that additional information within the guideline on criteria defining appropriate patients that would benefit from treatment, as detailed in the SmPC would be beneficial.[24] **Bladder Cancer** Since a small increased risk of bladder cancer has recently been recognized as being associated with pioglitazone use, the prescriber should incorporate the following into their routine medical practice when initiating pioglitazone therapy. •Pioglitazone is contraindicated in patients with current bladder cancer or a history of bladder cancer. •Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). •Pioglitazone is contraindicated in patients with uninvestigated macroscopic haematuria. Takeda is currently supporting a global ten-year epidemiological study by the U. of Penn. and	footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.

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					KPNC to investigate the relationship between pioglitazone and bladder cancer. The KPNC study was initiated based on preclinical studies showing bladder tumours only in male rats. The study protocol was reviewed by regulatory authorities including the European Medicines Association (EMA) and ongoing interim study results have been submitted to these regulatory agencies for review on a regular basis. Interim results of this study have been published previously. A five-year interim analysis had shown no overall statistically significant increased risk of bladder cancer among patients ever treated with pioglitazone, but did suggest an association between bladder cancer and increasing levels of pioglitazone exposure.[24] In the eight-year interim data, the magnitude of the previous associations became weaker, and no groups previously reported to have an association reached statistical significance in this analysis.[25] The KPNC study has now completed and final results are expected to be published within the coming months, when final conclusions from these data can be made on the risk of bladder cancer. **Fluid Retention and Congestive Heart Failure (CHF)** • Pioglitazone is contraindicated in patients with heart failure or a history of heart failure.	

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					• Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction, symptomatic coronary artery disease, or the elderly), physicians should start with the lowest available dose and increase the dose gradually. • Patients should be observed for signs and symptoms of heart failure, weight gain or oedema particularly those with reduced cardiac reserve. • Since insulin and pioglitazone are both associated with fluid retention, concomitant administration of pioglitazone and insulin may increase the risk of oedema. • Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Pioglitazone should be discontinued if any deterioration in cardiac status occurs. **Elderly Patients** • Combination use with insulin should be	

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					considered with caution in the elderly because of increased risk of serious heart failure. • In light of age-related risks (especially bladder cancer, fractures and heart failure), the balance of benefits and risks should be considered carefully both before and during treatment in the elderly. • Physicians should start treatment with the lowest available dose and increase the dose gradually, particularly when pioglitazone is used in combination with insulin.	
699	TAKEDA UK Ltd	Full NICE	General	General	**References** 1. Takeda UK Data on File (Alogliptin Periodic Safety Update Report, October 2014). 2. Nauck MA, *et al. Int J Clin Pract* 2009; 63: 46-55. 3. Pratley RE, *et al. Curr Med Res Opin* 2009; 25(10): 2361-2371. 4. Pratley RE, *et al. Diabetes Obes Metab* 2009; 11(2): 167-176. 5. Rosenstock J, *et al. Diabetes Obes Metab* 2009; 11: 1145-1152. 6. Bosi E, *et al. Diabetes Obes Metab*; 2011; 13(12): 1088-1096. 7. Del Prato S, et al. *Diabetes, Obes Metab* 2014; 16 (12): 1239-1246 8. DeFronzo R, *et al. Diabetes Care* 2008; 31 (12): 2315-7. 9. Pratley RE, *et al. Diabetes* 2012; 61 (Suppl	Thank you for the references.

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					1): A299. 10. Rosenstock J, *et al. Diabetes Obes Metab* 2013; doi: 10.1111/dom. 12102. 11. Vipidia Summary of Product Characteristics. Available from http://www.medicines.org.uk/emc. Last accessed March 2015. 12. Pratley RE, et al. *J Am Geriatr Soc* 2009; 57(11): 2011-2019. 13. White et al. *N Engl J Med* 2013; 369: 1327-1335. 14. Zannad F, et al. Poster presented at the meeting of the American College of Cardiology, Washington, DC. 29-31 March 2014. 15. Gibbs JP et al. J Clin Pharmacol. 2012 Oct;52(10):1494-505. Epub 2011 Dec 12 16. Aroda VR et al. Clin Ther. 2012 Jun;34(6):1247-1258.e22. doi: 10.1016/j.clinthera.2012.04.013. Epub 2012 May 18. 17. Eposito K et al. BMJ Open. 2015 Feb 16;5(2):e005892. doi: 10.1136/bmjopen-2014-005892. 18. Inzucchi S et al. *Diabetes Care* 2012; 35: 1364-1379 19. Craddy P, et al. *Diabetes Therapy* 2014; DOI 10.1007/s13300-014-0061-3. 20. NHS Rx: Copyright © 2013, Re-used with the permission of the Health and Social Care Information Centre. All rights reserved OGL	

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					Version 2. NHS Rx: Copyright © 2013, Re-used with the permission of the NHS Wales Shared Services Partnership. All rights reserved OGL Version 2. 21. http://www.hscic.gov.uk/article/4946/22-million-pounds-spent-every-day-on-diabetes-drugs-in-primary-care Last Accessed March 2015. 22. Scheen et al. *Diabetes Metab Res Rev*. 2010 Oct;26(7):540-9. 23. CSD Patient Data Qtr Dec 2014 24. Actos (pioglitazone) Summary of Product Characteristics. Available from www.medicines.org.uk, last accessed March 2015. 25. Relative Risk of Bladder Cancer with Pioglitazone for Diabetes Mellitus: An Updated 8-Year Interim Report of a 10-Year Follow-Up Study, August 28 at the ISPE meeting in Montreal	
67	The Royal College of Pathologists	NICE	18	1.6.2	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 feedback. The recommendation has been amended.
629	The Royal College of Physicians	NICE	General	General	The Royal College of Physicians (RCP) is happy to endorse the response submitted by the ABCD to the above consultation.	Thank you for your feedback.
265	The United Kingdom Clinical Pharmacy	Full	12	1 ,2	The information is very specific compared to the more patient orientated comments on the paragraph above (page 11, lines 33-36). This disparity in wording is a little confusing.	Thank you for your feedback. Recommendation 1.6.5 (in the NICE version; page 11, lines 33 to 36 in the full guideline) is meant to be generic and provide guidance on patient care in agreeing, setting and monitoring individual

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	Association					HbA1c targets. Recommendation 1.6.8 (in the NICE version; page 12, lines 1 to 4 in the full guideline) provides specific guidance on HbA1c threshold for drug intensification (that is 58 mmol/mol [7.5%]) and an associated HbA1c target of 53 mmol/mol (7%).
266	The United Kingdom Clinical Pharmacy Association	Full	15	algorithm	What happens to the patients that were initiated on repaglinide? At intensification does this stop, or do they move straight onto 3 agents? Would we really initiate 2 agents together? Would we not over burden the patients, risk poor acceptability and not being able to identify the implicated agent and losing the patients' confidence in the treatment plan. I can see from HbA1c perspective with each agent expected to reduce by on average 5-10mmol each that the overall control may benefit, but I think a detailed plan would be more appropriate than starting both at the same time. No mention of SGLT2 agents- although not common agent at present, primary care are using especially early in diagnosis period where the metabolic (weight loss) benefits are helping patients with their lifestyle choices and own weight loss management plans. This is made a little clearer in the wording on page 21 line 26	Thank you for your feedback. As stated in recommendation 1.6.23 (in NICE version for consultation) "*When switching from repaglinide to any of these combinations, introduce the 2 new medicines in a stepwise manner, checking for tolerability of each*", repaglinide should be stopped and switched. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-

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						references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
283	The United Kingdom Clinical Pharmacy Association	Full	166	algorithm	4 agent therapy? Algorithm stops at 3 agent therapy	Thank you for your feedback. No relevant evidence was identified at third intensification of treatment. In recognition of the lack of evidence at this intensification level, a research recommendation has been made. Given that no evidence has been reviewed for this stage of treatment, the guideline development group did not think it was appropriate to make recommendations for this phase of treatment intensification.
267	The United Kingdom Clinical Pharmacy Association	NICE Full	17 18	1.4.11 20	Thiazides are no longer recommended for BP control in line with NICE hypertension guidance.	Thank you for your feedback. The NICE hypertension guidance (CG127) recommendations published in 2011 do not extend to people with diabetes. Blood pressure therapy was not prioritised for update within this iteration of the type 2 diabetes guideline following the stakeholder workshop and stakeholder consultation during the scoping phase. As no new evidence reviews have been conducted, it is not possible to make any changes to these recommendations.
268	The United Kingdom	Full	18	10	Does the new hypertension guidance not suggest that ARBs should always be used in preference to ACEs for African and Caribbean	Thank you for your feedback. This is recommended as step 2 treatment in people of African or Caribbean family origin in the NICE

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	Clinical Pharmacy Association				people- (bradykinin reaction).	clinical guideline (CG127) on Hypertension (2011). However, the Hypertension guideline did not specifically include people with diabetes in the evidence base. Therefore, the Hypertension guideline cross refers to recommendations on blood pressure management in people with type 2 diabetes in the Type 2 diabetes guideline. This section of the type 2 diabetes guideline was not prioritised for update following the stakeholder workshop and stakeholder consultation during the scoping phase. The recommendations have been brought forward from the previous iteration of the guideline unchanged. As no new evidence reviews have been conducted, it is not possible to make any changes to these recommendations.
269	The United Kingdom Clinical Pharmacy Association	NICE Full	19 19	1.6.5 6	The ADA/EASD list a range of sensible options that would suggest setting a higher target. It would be worth recommending similar or referencing this list to provide further guidance.	Thank you for your feedback. The guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE version).
284	The United Kingdom Clinical Pharmacy Association	Full	199		High emphasis on sitagliptin.nil reference to other agents in the class. Agents that do not require dose adjustment for renal impairment are a useful tool in stabilising patients on treatment, and helping with confidence and adherence with medication regimens.	Thank you for your feedback. The Linking Evidence to Recommendations table (table 61, draft full guideline for consultation) summarises the deliberations of the guideline development group with respect to DPP-4 inhibitors that were included in the health economic model i.e. sitagliptin and vildagliptin. Studies on linagliptin and saxagliptin reported HbA1c outcomes only at

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						3 and 6 months and therefore were not included in the health economic model. Due to the wide credible/confidence intervals, no difference amongst the 4 drugs was observed in change in HbA1c at 3 and 6 months, hypoglycaemia, dropouts due to adverse events, total dropouts, nausea and change in bodyweight at 12 and 24 months. The rationale for recommending DPP-4 inhibitors as a class has been added in "Other considerations" and takes into account the overall clinical and health economic evidence. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
272	The United Kingdom Clinical Pharmacy Associatio	Full	20	26	Guidance on what to do as sick day rules and risk of AKI- should this be referred to (new guidance now available)	Thank you for your feedback. It is outside the scope of the type 2 diabetes guideline to look at specific advice and information to be given to people with chronic kidney disease (CKD). The NICE clinical guideline (CG182) on Chronic Kidney Disease was published in 2014 and

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	n					includes updated recommendations on risk factors associated with CKD progression and also advice and education for people with CKD.
273	The United Kingdom Clinical Pharmacy Association	Full	21	26	See comments in comment 2 above.[ID269]	Thank you for your feedback. The guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE version).
270	The United Kingdom Clinical Pharmacy Association	NICE Full	22 20	1.6.18 32	Consider recommending stopping metformin in patients with a baseline > 45 ml/min/11.73m2 who are at high risk or have a history of acute kidney injury.	Thank you for your feedback. The guideline development group considered the recommendation as worded provides adequate guidance on the care to be exercised in people with type 2 diabetes at risk of deteriorating kidney function.
274	The United Kingdom Clinical Pharmacy Association	Full	22	21	Would it be beneficial to offer some guidance about the benefits of each of the GLP-1 agents. So that treatments targeted to the groups that will benefit (patients with a loss in prandial response, and lower HbA1c appear to do well on lixisenatide (low acquisition cost), but the good response does not appear to be there for poorer starting control higher HbA1c patients, and those with overall reduction in fasting glucose too.)	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are

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						appropriate, choose the option with the lowest acquisition cost).
271	The United Kingdom Clinical Pharmacy Association	NICE Full	23 20	1.6.23 34	Using repaglinide as a first line option makes second line titration extremely tricky. It requires the patient to be started on two new medications, meaning that either both are started at the same time with a risk of ADEs or each must be initiated and titrated separately requiring an intensive time input from primary care. This wastes both time and money and is readily acknowledged by the GDG.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
275	The United Kingdom Clinical Pharmacy Association	Full	23	27	Really? Would this not be dependent upon the pattern of meals that the patient has? More individualisation n may be appropriate.	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
277	The United Kingdom	NICE	24	1.6.26	SGLT2 inhibitors are currently being recommended by NICE for monotherapy – this is not acknowledged by the guideline and	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug

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	Clinical Pharmacy Association	Full			therefore means that it is already out of date! In addition this class has renal restrictions and metabolic benefits that indicate they should be considered as first or second line therapy. By waiting until later this class will lose their beneficial profile. NB – this recommendation doesn't see to appear in the summary at the beginning of the full guideline.	therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
276	The United Kingdom Clinical Pharmacy Association	Full	24	15	Domperidone- would we still be stating this as a choice now that the cardiac issues and recent safety advice for longterm domperidone has been released.	Thank you for your feedback. This section of the type 2 diabetes guideline was not prioritised for update following a stakeholder workshop and stakeholder consultation at the scoping stage. **I**t was considered by the type 1 diabetes guideline and both guideline development committees agreed that the management of gastroparesis was likely to be similar between people with type 1 and type 2 diabetes. Therefore, 2 recommendations on the treatment of gastroparesis from the type 1 diabetes guideline have been adopted in the type 2 diabetes guideline. In the recommendations, domperidone is recognised as having the strongest evidence for effectiveness but that it should only be used in exceptional circumstances when neither metoclopramide or erythromycin have been effective, based on the recent safety issues highlighted by the MHRA.
278	The United Kingdom	NICE	26	1.6.30	Considerable evidence from ABCD audits have indicated that weight loss OR glycaemic control are beneficial for this population. This does not	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules

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	Clinical Pharmacy Association	Full	22	37	seem to have been considered and this recommendation is just a repetition of old technology appraisals.	that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
279	The United Kingdom Clinical Pharmacy Association	NICE Full	26 22	1.6.31 40	The use of GLP-1 agonists alongside insulin is now widely used and has a large volume of evidence behind it. It costs considerable resources to refer a patient for this alone – why has this not been considered?	The guideline development group noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
280	The United Kingdom Clinical Pharmacy Association	NICE Full	27 23	1.6.34 14 39	Insulin degludec does not appear to have been considered during this recommendation – why?? The recommendation regarding devices is outdated – analogues and NPH all come in the same devices now except the innolet which is usually preferred in elderly patients. This seems to be a pointless recommendation. The recommendation regarding analogue mixes for patients who prefer to inject immediately before meals means that this could be used by	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec–metformin

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					anyone without necessary consideration – and will result in hugely increased costs	was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec–metformin, and subsequently it does not appear in the algorithm.
285	The United Kingdom Clinical Pharmacy Association	Full	271	241	See comment 8[ID272] Guidance on what to do as sick day rules and risk of AKI- should this be referred to (new guidance now available)	Thank you for your feedback. It is outside the scope of the type 2 diabetes guideline to look at specific advice and information to be given to people with chronic kidney disease (CKD). The NICE clinical guideline on Chronic Kidney Disease was published in 2014 and includes updated recommendations on risk factors associated with CKD progression and also advice and education for people with CKD.
282	The United Kingdom Clinical Pharmacy Association	Full	81	31	Thiazides are no longer recommended for BP control in line with NICE hypertension guidance. [see comment 267]	Thank you for your feedback. The NICE hypertension guidance (CG127) recommendations published in 2011 do not extend to people with diabetes. Blood pressure therapy was not prioritised for update within this iteration of the type 2 diabetes guideline following the stakeholder workshop and stakeholder consultation during the scoping phase. Therefore the recommendations on hypertension from the previous iteration of the type 2 diabetes guideline have been retained.
281	The United Kingdom Clinical Pharmacy Associatio	Full	General	General	The initial therapy choices and intensification appear to be fraught with decisions based on interpretation of possible options There does not seem to be a 'standout' first line choice at any level of intensification and so the GDG have imposed choices rather than allow	**Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of the available evidence. The guideline development group has reflected on the clinical evidence for the**

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	n				individualisation. In addition the newer therapies have not been appropriately considered alongside the standard choices, for example DPP-4 inhibitor evidence at initial therapy level seems to be entirely based on sitagliptin – which is similar but not identical to others in the class. Whilst the choices seem to be made with the best of intentions it seems highly inappropriate.	**recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.**
189	Training, Research and Education for Nurses in Diabetes	NICE	11	15	HbA1c targets of 53 mmol/mol (7%) may increase the numbers experiencing hypoglycaemia and subsequent ambulance callout and particularly if used in people with a long duration of diabetes, those with renal impairment, the frail and /or older people.	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
190	Training, Research and Education for Nurses in Diabetes	NICE	11	23 -25	This will include older people including the frail elderly, and drivers if Rapaglinide is prompted as first or 2nd line treatment - Hypo information will need to be given and leaflets along with blood glucose monitoring equipment and training	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The recommendations and algorithm have been

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						simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration.
191	Training, Research and Education for Nurses in Diabetes	NICE	12	8	This medication (Rapaglinide) is strongly associated with hypoglycaemia - so individuals may need to blood glucose monitor - any cost saving would therefore be lost. and particularly if the user has a severe hypo leading to ambulance call out or hospital admission Does the panel think that this and Sulphonylureas should come with a warning about using it in dosett boxes as the patients who use these are not likely miss taking these take drugs if they do not eat and so are more at risk of hypoglycaemia The manufacturers of Repaglinide's own guidance states driving guidance as: "If you are a driver you should take special care, as your ability to concentrate may be affected if your diabetes is not well controlled. You may be advised to check your blood sugar levels before you travel and to have a snack with you on long journeys".	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated.
192	Training, Research and Education for Nurses	NICE	12	9	The addition of Pioglitazone in this predominately older population is a real risk – as heart failure rates in people with diabetes are increasing year after year (Diabetes UK State of the Nation 2015).	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the

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	in Diabetes				This drug should also be used in caution in post-menopausal women due to risk of bone fractures- as in the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). In view of this evidence the number of patients it could be recommended for is limited	appropriateness and implementability of these recommendations and associated algorithms. As per NICE guidance, the guideline assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
193	Training, Research and Education for Nurses in Diabetes	NICE	13	14	This section is too vague- Please can you add in more specific information re co-morbidities and glycaemic targets in line with other national and international guidance such as Diabetes UK-End of life guidance, The ADA medical standards 2015, The IDF care of older people with type 2 DM, The Association of Geriatricians 2013	Thank you for your feedback. Consideration was given to being more specific in this section. However, this was balanced against the need to ensure that the approach to care is individualised, taking into account a range of patient specific factors. The need for indivualisation of care, and the wide range of factors that need consideration prevented the creation of more specific information.
194	Training, Research and Education for Nurses in Diabetes	NICE	19	25	Have you considered the risk of hypoglycaemia in people with diabetes trying to attain these targets (53 mmol/mol, 7%) if on insulin, Rapaglinide or Sulphonylureas(SU)	Thank you for your feedback. The guideline development group agrees that an HbA1c target of 53 mmol/mol (7%) may not be appropriate for certain individuals and therefore has included recommendations that account for individualised target setting (see recommendations 1.6.5 and 1.6.9 in the NICE version). Recognition of the appropriateness of targets and importance of considering individual's circumstances are

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						documented in the Linking Evidence to Recommendations table (see section 8.1.3 in the full guideline).
196	Training, Research and Education for Nurses in Diabetes	NICE	20	10	The use of SU and now of Rapaglinide will mean any small cost savings made using these drugs for most with Type 2 DM will easily be offset with costs related to ambulance call outs and hospital admission	Thank you for your feedback. NHS costs relating to severe hypoglycaemic episodes were fully considered in the health economic modelling (see full guideline 8.4.3). These included estimates of the proportion of severe hypoglycaemic episodes that required GP admissions, ambulance call outs, A&E attendance and/or hospital admissions.
197	Training, Research and Education for Nurses in Diabetes	NICE	20	15	What does this sentence actually mean - see previous comments	Thank you for your feedback. As indicated by multiple stakeholders, people who are older or frail may be at a greater risk of tight glycaemic control. Hence, the recommendation highlights that specific consideration should be given to these clinical circumstances.
198	Training, Research and Education for Nurses in Diabetes	NICE	20	18	The amount of patients accessing emergency care for hypos due to low HbA1c's is increasing as are admission rates - a range for HbA1c targets for those using insulin Rapaglinide and SU should be stated which identifies glycaemic control recommendations according to different patient. It is known that SUs can account for up to one third of A/E attendances, largely confirmed to the older and frail patient group (Rajendran R, Hodgkinson D, Rayman G. Patients with diabetes requiring emergency department care for hypoglycaemia: characteristics and long-tern outcomes	Thank you for your feedback. NHS costs relating to severe hypoglycaemic episodes were fully considered in the health economic modelling (see full guideline 8.4.3). These included estimates of the proportion of severe hypoglycaemic episodes that required GP admissions, ambulance call outs, A&E attendance and/or hospital admissions.

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					determined from multiple data sources. *Postgrad Med J* 2015 (in press). http://dx.doi.org/10.1136/postgradmedj-2014-132926	
195	Training, Research and Education for Nurses in Diabetes	NICE	20	5	This section needs to be more specific in respect of reduced life expectancy - there should be no HbA1c targets for individuals experiencing the last year of life (See Diabetes UK, ADA and European guidance) People in care homes with or without dementia are now considered as being in end of life care as are the frail elderly – the ADA and IDF offer specific information on glycaemic targets for those with other comorbidities and this information is clearly needed in the UK documentation	Thank you for your feedback. The recommendation provides general guidance on circumstances in which consideration should be given to relaxing blood glucose targets. The guideline development group has not reviewed evidence on the withdrawal of HbA1c targets for people with reduced life expectancy and did not consider it appropriate to provide specific guidance in the absence of evidence.
199	Training, Research and Education for Nurses in Diabetes	NICE	21	3	This could mean most people with Type 2 DM on SUs or Rapaglinide who drive will need to test	Thank you for your feedback. The recommendation notes that individuals on oral medications that may increase the risk of hypoglycaemia while driving or operating machinery should be considered for self-monitoring as per the DVLA guidance.
200	Training, Research and Education for Nurses in Diabetes	NICE	21	8	Diabetes and steroids - Please check the JBDS management of hyperglycaemia for people taking Gluco-corticosteroids – who recommend that all on diabetes treatments should be blood glucose testing	Thank you for your feedback and reference.
20	Training,	NICE	22	11	Please state where Metformin sustained release	Thank you for your feedback. The guideline

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Stakeholder comments table with responses

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1	Research and Education for Nurses in Diabetes				fits in with this?	development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated.
202	Training, Research and Education for Nurses in Diabetes	NICE	22	13	Please see previous comment - there should be provisos on the individuals where Rapaglinide or Sulphonylureas would not be suitable – Also the licence for use is very limited and complicated. The dose range is wide and means patients will need to take multiples of tablets which may lead to non-concordance. The ADA have an excellent algorithm showing side effects of all drug classes which if replicated for the UK would benefit HCPs in the decision making process	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
203	Training, Research and Education for Nurses	NICE	22	25	Please state patients who would be at increased risk of hypos and or weight gain when using the SU- Also please advise on the use of a SGLT-2 inhibitor and where it sits in this pathway	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the

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	in Diabetes					appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
205	Training, Research and Education for Nurses in Diabetes	NICE	23	22	Where do SGLT-2 Inhibitors fit in or GLPI receptor agonists?	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the

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						technology appraisal guidance according to the normal process for assessing the need to update TA guidance. Please see recommendations 1.6.29, 1.6.30 and 1.6.31 in the NICE version for the position of GLP-1 mimetics.
204	Training, Research and Education for Nurses in Diabetes	NICE	23	3	Is the drug with the lowest acquisition cost the most effective?	Thank you for your feedback. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
206	Training, Research and Education for Nurses in Diabetes	NICE	24	3	Use of Pioglitazone – There should be proviso's around it use such as : Or if the individual has heart failure or previous history of bladder cancer or is post menopausal	Thank you for your feedback. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm.
207	Training, Research and	NICE	24	General	The use of SGLT-2 s - Can you be more specific about the use of these agents in reducing HbA1c and in reducing weight as HCPs will not	Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug

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	Education for Nurses in Diabetes				want to keep checking all the different guidelines as they have limited consultation time	therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the normal process for assessing the need to update TA guidance.
208	Training, Research and Education for Nurses in Diabetes	NICE	25	10	Please be more specific around the licensing for non oral diabetes drugs The licenses are different for all these agents so the lowest cost drug many not be suitable for all	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
209	Training, Research and Education for Nurses in Diabetes	NICE	25	26	Do you mean sleep apnoea if so please be specific	Thank you for your feedback. The guideline development group considered the generic phrase "other medical problems associated with obesity" adequate, not requiring an exhaustive list of examples of relevant conditions.
211	Training, Research and Education for Nurses in	NICE	26	10	If the patient has lost the weight and not reduced HbA1c there are still health benefits re cardiovascular that should be taken into account- equally any reduction in HbA1c is good – please consider changing the guidance to either HbA1c or weight loss as an indication for	Thank you for your feedback. The guideline development group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the

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	Diabetes				continuing on treatment	guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87.
212	Training, Research and Education for Nurses in Diabetes	NICE	26	12	Why not intermediate care? Suitably trained HCPs in intermediate care or enhanced practice are capable of caring for these individuals	Thank you for your feedback. The guideline development group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics.
213	Training, Research and Education for Nurses in Diabetes	NICE	26	27	Suggest include insulin safety advice and driving advice in this section	Thank you for your feedback. Referral to DVLA guidance has been added to the recommendation
210	Training, Research and Education for Nurses in Diabetes	NICE	26	6	Are they all equally effective? There is evidence that the cheapest is not always the most effective	Thank you for your feedback. A generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest

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						acquisition cost).
214	Training, Research and Education for Nurses in Diabetes	NICE	27	9	Where does Insulin Degudec fit in with this guidance?	Thank you for your feedback. At second intensification, insulin degludec was evaluated in combination with metformin, along with all other insulin combinations that met the review's inclusion criteria (see full guideline for range of insulins that were evaluated at second intensification, section 8.4.12). The modelled treatment effects for HbA1c, weight change, drop outs and hypoglycaemia can be found in appendix F table 58. Insulin degludec-metformin was not considered to be cost-effective compared to other treatment options. Therefore, the guideline development group chose not to recommend insulin degludec-metformin, and subsequently it does not appear in the algorithm.
215	Training, Research and Education for Nurses in Diabetes	NICE	30	10	There needs to be specific clear guidance on diabetes and CKD in this document and especially around screening and monitoring ; and also the use of oral diabetes medications where dose reduction or use with caution or non use depending on CKD function varies between same class medication This guidance signposts the reader to the July 2014 Renal guidance for care of people with diabetes- the Renal guidance signposts back to the CG 66/ 687 so in both no information is provided Guidance of when to refer to specialist care and treatment plans are clearly needed in both NICE guidelines	Thank you for your feedback. The recommendations on chronic kidney disease have been updated by the recently published guideline on Chronic Kidney Disease. NICE anticipates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. This function links all related NICE guidance on a topic area and should assure quick navigation between recommendations on type 2 diabetes and chronic kidney disease.

Type 2 diabetes (update)

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216	Training, Research and Education for Nurses in Diabetes	NICE	General	General	This guidance is at complete odds with all other international and some UK specific guidance – the pathways are confusing as is the treatment algorithms in the full guidance and will only HCPs working with individuals with diabetes. The use of medications which can lead to hypoglycaemia or weight gain without deference to clear safety information is concerning as is the unclear guidance on glycaemic targets – The ADA information regarding agreed targets depending on clinical need, co-morbidities and other factors such as motivation, duration of diabetes is clear and concise and it would be beneficial if this was in this UK guidance As this draft recommendation stands, justifying the conclusions made and teaching and training in particular with non-specialist clinicians, when the guidance is not in alignment with other international recommendation would be challenging and probably inappropriate	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines. The guideline recommends 2 HbA1c targets: 1) 48 mmol/mol (6.5%) for people managed on diet/lifestyle or in combination with a single drug not associated with hypoglycaemia (see recommendation 1.6.7 in NICE version). 2) 53 mmol/mol (7%) for people who require drug intensification (see recommendation 1.6.8 in NICE version). However, the guideline development group recognises that there may be circumstances where the recommended targets are not appropriate and has therefore included recommendations 1.6.5 and 1.6.9 (in the NICE version) to individualise and agree targets. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia in light of stakeholders' feedback on the appropriateness and implementability of

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						these recommendations and associated algorithms. The recommendations and algorithm have been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
217	UK National Screening Committee	NICE	General	General	The UK NSC does not have any comments	Thank you for your feedback.
85	University Hospitals Birmingham NHS Foundation Trust	Full	General	General	The type 2 diabetes guidelines by the Group are a way forward in combatting this epidemic. The educational element of the guidance is good and tackles an important issue. One of the difficulties we had in our clinical practice was to get the patients attend educational sessions. Hence it is important to look at the evidence in real life situation and alter the programme accordingly. The economic modelling for structured education is based on 2 papers whiles the studies from outside UK that have been	Thank you for your comment. Education and dietary/lifestyle interventions were not prioritised within the guideline for update. This decision was taken following a workshop conducted with stakeholders during the scoping of the guideline and stakeholder consultation.

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					discarded. Hence it is important that the structured education element needs to looked carefully before investing huge amounts as the programme will need to demonstrate adequate short-term and long-term outcomes with good concordance of attendance. The blood glucose monitoring advice to only patients on sulphonylureas and insulin's is proper and saves cost of unnecessary glucose monitoring. No health economic modelling paper for dietary intervention. Most studies used for dietary intervention their primary end point was weight loss with glycaemic improvement being a secondary outcome.	
86	University Hospitals Birmingham NHS Foundation Trust	Full	General	General	The guidance around drug therapy and the intensification charts are confusing and at time contradictory to the current ADA/EASD guidelines (Published Diabetes Care 2015) and the clinical practice in UK. All the economic modelling for drug therapy is based on UKPDS without considering recent important trials like VADT/ACCORD. The emphasis of the economic modelling is on HbA1c reduction while important disutility's like Hypoglycaemia and Weight gain are discounted. This has created a treatment algorithm in which "cheap-wins" while "cost-effectiveness loses". Repaglinide as a therapy is hardly used in the UK and is not a part of the treatment algorithm.	Thank you for your feedback. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling, which sets this guideline apart from other internationally recognised guidelines. The guideline development group has reflected on the clinical evidence for the recommendations related to the pharmacological management of hyperglycaemia

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					Based on very little clinical evidence (2 studies) and a questionable network Meta-analysis it has been proposed as the preferred first line in Metformin intolerant patients and second line in most cases. The fact this agent needs to be given three times a day will have an effect on concordance especially in elderly and BME groups were compliance is an issue. It also will require more frequent blood glucose monitoring adding to the cost of strips and frequency of Hypo's. University Hospital Birmingham has one of the highest rates of admissions with severe Hypoglycaemia in the country. We have a large BME and elderly population in whom this would be an issue. The cost of all Hypo has been calculated at £350/ this is gross underestimation and does take into account studies like UK Hypoglycaemia study. The cost of sever Hypo specially requiring hospital admission is much higher. Although the evidence showing exact economic cost is not available it should be explored further and if need be extrapolating the data from overseas studies. Pioglitazone as a drug has a definite place in the diabetes armamentarium but making it a drug of choice for second intensification is controversial to say the least. Although Pioglitazone has a place in therapy for a selected group of patient making its use universal is not good. There have been question raised about Pioglitazone with regards to congestive cardiac failure,	in light of stakeholders' feedback on the appropriateness and implementability of these recommendations and associated algorithms. The guideline development group has recommended the use of metformin modified-release in circumstances where standard-release metformin is not tolerated. The group has also given equal weighting to DPP-4 inhibitors, pioglitazone, repaglinide and sulfonylurea where metformin is contraindicated or not tolerated. At first intensification, the guideline development group has recommended the following metformin-based dual therapy options: metformin+pioglitazone, metformin+sulfonylurea and metformin+DPP-4 inhibitor; and for people who cannot take metformin: pioglitazone+sulfonylurea, pioglitazone+DPP-4 inhibitor and sulfonylurea+DPP-4 inhibitor. A footnote on MHRA guidance on safety alerts for pioglitazone and advice to exercise particular caution if the person is at high risk of the adverse effects of the drug has been added to the recommendations and algorithm. Relevant studies meeting the review's selection criteria that examined GLP-1 mimetics in combination with basal insulin were not identified at the cut off search date of June 2014. Any studies published after this date could not be included in this update. Based on the updated evidence review and health economic analysis, the guideline development group noted that there

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					osteoporosis in pre-menopausal women and bladder cancer risk. The fact that it causes weight gain in nearly all patients again is an important consideration. The place of therapy of Pioglitazone again seems to be based on economic modelling on Hba1c while discounting factors like weight gain. For the Network Metanalysis the DPP-4 inhibitors and GLP-1 analogues are treated separately but in the conclusions the findings of the NMA are ignored. They are all clubbed together with remarks that the choice should depend on the lowest acquisition cost. The emerging clinical evidence and clinical practice shows that there difference among these agents both in their clinical effectiveness and perhaps long-term outcomes (although trial results are awaited). The SGLT-2 inhibitors have got their own HTA's but in the treatment algorithm their place in therapy seems to be not clear. For the economic analysis it is claimed that "Non-UK based studies excluded 81 CUA's identified 79 excluded as Pharma sponsored and the 2 included HTA found older treatments were more cost effective than newer ones". No satisfactory explanation is given as to why this approach was taken. In summary the NICE Draft guidelines by the Group was a great opportunity to take the diabetes care in the UK forward but	was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The group discussed the phrasing of "specialist care setting" so as to not imply that the treatment combination can only be prescribed in secondary care. The guideline development group agreed that the phrase "specialist care advice with ongoing support" with examples of health care professionals provided greater clarity on the type and level of support and efficacy monitoring needed in prescribing insulin and GLP-1 mimetics. The group noted the high costs of GLP-1 mimetics and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the guideline development group chose to retain only the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous iteration of the guideline, CG87. Thank you for your comment on how the NICE technology appraisal guidance on SGLT-2 inhibitors fits within the broader pathway of drug therapy outlined in the guideline. Cross-references within the guideline have been revised to make this clearer, and the Technology Appraisal team at NICE will consider whether the changes to the guideline require changes to the technology appraisal guidance according to the

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					unfortunately the guidance produced is disappointing, based on weak evidence and flawed network meta-analysis. The cost-effectiveness argument seems to have taken a back seat to cost saving which is contrary to the principle on which NICE was established. As Clinicians managing people with diabetes we have got concerns about this guideline as it will take the diabetes care back in the UK by decades. We urge the NICE committee to re-examine the data and evidence with inputs Diabetes expert to come up with a good guidance that will augur well for people with diabetes in the long-term. References: 1. Type 2 diabetes: guideline consultation 2015. https://www.nice.org.uk/guidance/gid-cgwave0612/resources/type-2-diabetes-guideline-consultation2 (Accessed January 2015) 2. Khunti, K, Gray LJ, Skinner T, *et al*. Effectiveness of a diabetes education and self-management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. *BMJ* 2012;**344**:e2333. http://dx.doi.org/10.1136/bmj.e2333	normal process for assessing the need to update TA guidance. The recommendations and algorithm have also been simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Specifically, a generic recommendation has been added and emphasised in the algorithm to base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). The selection of and limitations within the UKPDS OM1 were fully considered by the guideline development group (see appendix F 3.1 and 5.2.2). Cost-effectiveness modelling for NICE includes dropouts due to adverse events, weight changes and hypoglycaemia as well as HbA1c (see 8.4.3 in the full guideline). Costs associated with severe hypoglycaemia were detailed in appendix F 3.9.4. As explained in appendix F 2.2, non-UK based CUAs were excluded due to the existence of UK

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					3. Deakin TA, Cade JE, Wiliams R, Greenwood DC. Structured patient education: the Diabetes X-PERT Programme makes a difference. *Diabet Med* 2006 23;**9**:944-54. http://dx.doi.org/10.1111/j.1464-5491.2006.01906.x 4. Farmer A, Wade A, Goyder E, *et al*. Impact of self-monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007;**225**:132. http://dx.doi.org/10.1136/bmj.39247.447431.BE 5. Viberti G, Kahan SE, Greene DA, *et al*. A diabetes outcome progression trial (ADOPT): an international multicentre study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 2002;**25**:1737-43. http://dx.doi.org/ 10.2337/diacare.25.10.1737 6. Leese GP, Wang J, Broomhall J, *et al*. for the DARTS/MEMO Collaboration. Frequency of severe hypoglycaemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 2003;**26**:1176-80. http://dx.doi.org/	based evidence. No CUAs were excluded on the basis of their funding source.

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					10.2337/diacare.26.4.1176 7. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;**50**;1140-7. http://dx.doi.org/10.1007/s00125-007-0599-y 8. Thong KY, Gupta PS, Cull ML, *et al*. GLP-1 receptor agonists in type 2 diabetes – NICE guidelines versus clinical practice. *Br J Diabetes Vasc Dis* 9. . Skyler JS, Bergenstal R, Bonow RO, *et al*. Intensive glycaemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;**32**:187-92. http://dx.doi.org/10.2337/dc08-9026 10. Inzucchi SE, Berganstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes, 2015: A patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes*	
88	Weight	Full	12	2	Before reinforcing advice about diet etc, perhaps	Thank you for your feedback. It is envisaged that

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	Watchers	(NICE)	(19)	(1.6.8)	healthcare professionals could be prompted to discuss any challenges and barriers the patient is facing in managing their HBA1c, and then working in a patient centred manner to address these.	treatment selection is discussed and agreed with the patient and therefore, consultation would typically encompass the issues surrounding difficulty in controlling HbA1c. The guideline contains a recommendation on individualised care which should prompt healthcare professionals to support people with type 2 diabetes to manage their HbA1c in a holistic manner.
91	Weight Watchers	NICE	15	1.3/ General	Weight Watchers were disappointed to note that the section on Dietary Advice will not be updated to include more recent recommendations. In particular, there is no guidance on how patients are to be supported in achieving a weight loss target of 5-10%. For a more cohesive set of guidance, we recommend the consideration of adding a link referring to NICE PH53.	Thank you for your feedback. Dietary advice was not prioritised for update within this iteration of the guideline following the stakeholder workshop and stakeholder consultation during the scoping phase. However, based on the suggestion, a cross reference within the type 2 diabetes guideline to weight management NICE guidance such as PH53 has been added.
89	Weight Watchers	Full	17	4 -23	Weight Watchers would welcome the inclusion of a recommendation to refer patients to a suitable weight management intervention as recommended in PH53. An effective, evidence-based weight management intervention could prove beneficial for patients with type 2 diabetes to promote weight loss and ultimately improve their condition and the management.	Thank you for your feedback. A cross reference to related guidelines including PH53 has been added to the section on dietary management in the type 2 diabetes guideline.
90	Weight Watchers	Full	32 -33	General	Weight Watchers welcomes the emphasis on patient centred care. In addition the points made in this section, NICE may wish to consider signposting to the evidence based NHS patient decision aids on poorly controlled diabetes	Thank you for your feedback. These tools have been flagged to the NICE implementation team. Having looked at these tools further, they have shown a decision is pending on them in 2015. Once these tools have been updated, NICE

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					http://sdm.rightcare.nhs.uk/pda/diabetes-improving-control/ and improving diabetes control http://sdm.rightcare.nhs.uk/pda/diabetes-additional-treatments-to-improve-control/	would like to invite them to submit the resource to the NICE endorsement programme and/or the local practice collection for consideration and assessment of whether they are an example of implementation of NICE guidance.
87	Weight Watchers	Full	General	General	Weight Watchers is delighted by the conituning importance placed on patient pscychoeducation, and the additional guidance that is included on this topic.	Thank you for your feedback.
218	West London Mental Health NHS Trust	NICE	General	General	The document makes no reference to the identification and management strategies for Pre-diabetes. If this is no longer a helpful diagnosis it would be important to clarify this in the guidelines	Thank you for your feedback. It was not within the scope if the guideline to look at identification and management strategies for pre-diabetes. However, NICE had produced 2 pieces of public health guidance on preventing type 2 diabetes in those at high risk and also guidance on population and community-level interventions for this purpose.
779		Full	176	20	The baseline utility level was taken from the UKPDS study, however this is assumed to be the same for all intensification steps. Further research needs to be conducted into the baseline QoL of people at different stages of their diabetes.	Thank you for your feedback. This limitation was noted in appendix F (5.2.2).
653		Full	36 section 3.3.1 et seq:	l 29 et seq	It is not made clear this section and the next refers to surrogate outcomes and perhaps adverse events and not to true health outcomes. When considering true outcomes (notably vascular disease) a different time series would be used extending perhaps from 3 years to 30 years or more. Thus UKPDS and a few studies since.	Thank you for your feedback. While HbA1c is a surrogate outcome, other true health outcomes such as hypoglycaemia, weight gain and adverse events have been considered. It is necessary and well accepted that the best available method of predicting microvascular and macrovascular complications is by extrapolation from surrogate outcomes like HbA1c.

Type 2 diabetes (update)

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