Type 2 Diabetes in adults
Consultation on draft guideline - Stakeholder comments table
26 June 2015 – 24 July 2015

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

ID	Type	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
137	Non Reg SH	Article published in the Lancet	General	General	General	The revised NICE draft type 2 diabetes guideline (June 2015) has been released for further consultation.[1] Some positive changes have been made since the first draft in January 2015, especially regarding the need to discuss and respond to patient preferences.[2] However, we believe the revised guideline remains unfit for purpose and is a missed opportunity to improve the lives of patients with type 2 diabetes (T2DM). If sanctioned by NICE, the guideline will be confusing and unworkable in busy clinical practice. It may also diminish the international reputation of NICE and reduce the influence of UK practice on the global management of T2DM.	Thank you for your feedback. The guideline development group has considered the issues raised by stakeholders at the second consultation, particularly with respect to the pharmacological management of blood glucose and have made further amendments to the algorithm and recommendations to facilitate evidence-based guidance that is user-friendly to a wide range of stakeholders including non-specialists.
138	Non Reg SH	Article published in the Lancet	General	General	General	Little has changed in the guideline regarding advice on drug treatment to control blood glucose despite, and contrary to, the advice of most leading specialists in the field.[2] The guideline adopts a step-up, "waiting for failure" approach and still only recommends intensification when HbA1c is 7.5% (58 mmol/mol) or greater. Yet it is widely accepted that in younger, more recently diagnosed patients, lower HbA1c levels should be targeted and achieved more rapidly, whilst for the elderly it should be 'older, higher, slower' (ADA and ABCD guidelines).[2] Unfortunately, sulphonylureas still feature prominently in the guideline's advice for all stages of intensification, despite the downsides of weight gain and hypoglycaemia and ongoing concerns regarding	Thank you for your feedback. Following the first consultation, the guideline development group (GDG) considered the stakeholders' feedback on the appropriateness and implementability of the blood glucose management recommendations and associated algorithms. While taking into account the evidence base, these recommendations and algorithms were simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. For example, • at initial therapy, metformin-modified release was added as an alternative when

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						cardiovascular safety.	standard-release metformin is not tolerated. • for people who are contraindicated or intolerant of metformin, the following are equal options: dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas. A footnote has now been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification. • a footnote on the safety alerts for pioglitazone was added, and a note to exercise particular caution if the person is at high risk of the adverse effects of this drug. • a cross-referral to NICE technology appraisal guidance on SGLT-2 inhibitors was added. • a generic recommendation was 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 GDG disagrees that the guideline promotes clinical inertia. Within the guideline, regular review with reinforcement of diet, lifestyle and adherence to treatment is recommended, along with consideration to stop ineffective medicines. The GDG also recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels. The GDG disagrees that sulfonylureas in particular are prominently placed in the recommendations and algorithm. Other antihyperglycaemic drugs are also associated with weight gain, hypoglycaemia and cardiovascular safety.

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139	Non Reg SH	Article published in the Lancet	General	General	General	NICE appraisals rely heavily on complex network meta-analyses (NMAs), and yet few clinicians have the training or mathematical skills to understand these nor to question how the data are derived. NMAs can have value, but they require meticulous selection of high-quality publications to avoid misleading results. Perhaps this reliance on NMAs explains the recommendation for repaglinide (with its potential for weight gain and hypoglycaemia, lack of evidence of sustainability or outcome data) as a first-line treatment in those intolerant of metformin.[2]	Thank you for your feedback. Network meta-analyses of randomised studies are preferred as it allows retention of focus on differences between randomised cohorts. Studies up to the cut off search date of June 2014 meeting the review's selection criteria were included, with sensitivity analyses undertaken and quality considered in GRADE assessments. Studies on repaglinide were checked (for example, dropouts) and not found to be systematically different from included studies of other antihyperglycaemic drugs. For people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas are recommended as equal options. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
140	Non Reg SH	Article published in the Lancet	General	General	General	For the repaglinide recommendation, the NICE advisory group considered seven papers on repaglinide monotherapy. Two studies reported on the same cohort of 100 patients from Pakistan,[3,4] duplicated in the same journal, whilst the third was a short-term pilot study on 60 patients from China.[5] These trial populations are totally	Thank you for your feedback. Nine repaglinide studies met the review's selection criteria at initial therapy, of which 8 provided usable data (i.e. data included measures of dispersion). Of these 8 studies, 2 were conducted in USA, 2 in Italy, 2 in Pakistan, 1 in China and 1 in 13

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						unrepresentative of the UK T2DM population, given their relatively young age and low BMI. Any clinician reading the remaining publications would conclude that repaglinide is a short-acting, "sulphonylurea-like" agent with similar efficacy, weight gain and hypoglycaemia. Furthermore, repaglinide is recommended as a 3 times per day meal-related dosing, which is highly likely to reduce adherence.[2]	different countries. Sample sizes ranged from 60 (China) to 576 (USA), with a total sample size of 1993. The mean age and BMI of participants in these 8 studies were 55 years (range 46-74 years) and 28kg/m^2 (range 26-30kg/m^2) respectively. Compared to the overall 114 studies included at initial therapy (see section 8.4.4.1 in the full guideline), of a total of 36,938 participants, the mean age ranged from 45.6 to 74.4 years and the mean BMI ranged from 23.2 to 39.8 kg/m^2. The 2 studies from Pakistan are different. Shah (2011) included 200 people and was conducted from September 2005 to September 2006, while Saleem (2011) included 100 people and was conducted from March 2006 to March 2007. Notwithstanding, only Saleem (2011) provided data for change in HbA1c. Further details of included studies are located in Appendix E.
141	Non Reg SH	Article published in the Lancet	General	General	General	The revised draft guideline still strongly supports pioglitazone as a second-line agent to metformin. Yet few patients would be happy to take this drug over safer, albeit more expensive, alternatives once told of the likelihood of weight gain, fluid retention, increased risk of congestive cardiac failure, as well as concerns over fractures and bladder cancer.[6] These potential adverse	Thank you for your feedback. For people who can take metformin and require intensification, three options are available, which are listed alphabetically: • metformin + a dipeptidyl peptidase-4 (DPP-4) inhibitor • metformin + pioglitazone

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						effects are poorly understood and, particularly in an elderly population, make the use of this agent questionable in an economy that can afford safer alternatives. In our professional opinion, pioglitazone still has a place in therapy, but only when other oral agents have failed and only with careful monitoring.	• metformin + a sulfonylurea It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. Given concerns over the safety of pioglitazone, a footnote on the safety alerts was added following the first consultation, with a note to exercise particular caution if the person is at high risk of the adverse effects of this drug.
142	Non Reg SH	Article published in the Lancet	General	General	General	Once again, the revision endorses the use of GLP-1 receptor agonists (GLP-1RA), but with a cut-off for use in patients with BMI >35kg/m^2,[1] a classification of severe obesity that NICE appears to have chosen on cost containment grounds with no evidence base to support it. There is the 'get out of jail free' clause that they can be used at a lower BMI where "weight loss would benefit other significant obesity-related comorbidities". Given the weight of evidence that weight loss is cardinal to reducing insulin resistance, and improving diabetes control and long-term outlook,[7] it is a missed public health opportunity not to have lowered the BMI cut-off for use of GLP-1RAs to 30 kg/m^2 in white Europeans and 27.5 kg/m^2 in Black and South Asian patients. Furthermore, the recommendation to discontinue treatment after 6 months unless both HbA1c and weight loss	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely

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						criteria are met will penalise the many patients who greatly improve their HbA1c, but do not achieve the required weight loss, and those who lose weight,[8] but do not reach the HbA1c threshold. In both scenarios, clinicians (and their patients) would consider GLP-1RA therapy a success. In an NHS committed to a 'duty of candour',[9] there needs to be more transparency in justifying these cut-offs to patients and practitioners.	to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Reference to the 2013 published NICE public health guidance (PH46) on "Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK" is made available in section 3.2 of the NICE short version.
143	Non Reg SH	Article published in the Lancet	General	General	General	While the revised guidelines acknowledge the existence of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors by appending a footnote to the	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2)

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						algorithms on intensification of treatment for T2DM, there is no attempt to incorporate these into an overall guidance package. The idea that a new NICE guideline can effectively ignore a class of oral antidiabetes agents that have been available in the UK for more than two years does not make sense (and is in stark contrast to the recent joint US and European Guidelines). How are interested general practitioners (the major focus of this guidance) meant to make sense of this?	inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring ways of presenting this information.
144	Non Reg SH	Article published in the Lancet	General	General	General	When intensification to insulin is necessary, isophane insulin is still recommended as first-line insulin therapy on grounds of cost, even though once-daily long-acting analogues are equivalent in efficacy and associated with less hypoglycaemia (particularly nocturnal hypoglycaemia).[10] In our opinion, for a guideline to wait until patients have their first serious hypoglycaemic event before they are allowed the "safer" alternative insulins is against the basic principles of our profession. It also begs the question as to why long-acting analogues are recommended as a first-line option for type 1 diabetes (current draft guideline), but denied to people with T2DM.	Thank you for your feedback. The recommendations are based on the evaluated clinical effectiveness evidence review and health economic analyses in people with type 2 diabetes and it would be inappropriate to extrapolate the recommendations from the type 1 diabetes guideline. The guideline development group (GDG) agreed that type 1 diabetes is a different condition to type 2. For example, individuals with type 1 diabetes are more likely to develop hypoglycaemia as they are more insulin sensitive and usually of lower BMI, when compared to individuals with type 2 diabetes who are usually more insulin resistant and have larger BMI. Moreover, the doses of insulin needed for type 2 diabetes may be much higher than for type 1 and hypoglycaemia in type 2

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							diabetes only becomes similar to the pattern of type 1 diabetes after about 5 years on insulin treatment. Given the differences, the GDG agreed that it would be inappropriate to extrapolate from the type 1 diabetes guideline for insulin therapy. The GDG noted that metformin–NPH insulin was consistently ranked in at least the top third for reducing HbA1c levels, hypoglycaemic events and change in body weight. In addition, of the assessed insulin-based options, NPH insulin was shown to be the most cost effective. While other metformin–insulin treatment options (such as metformin–insulin detemir) incurred lower costs and lost fewer quality-adjusted life years (QALYs) due to hypoglycaemic episodes, these gains were not enough to outweigh lower glycaemic efficacy (and associated long-term complication costs and QALYs) and increased treatment costs of the more expensive metformin–insulin options (see appendix F, section 4.9.2) The GDG recognised that there were other insulin–metformin combinations that had variable degrees of clinical effectiveness across the 3 outcomes, but were not as cost effective, such as metformin–detemir ranked in the bottom third for change in

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							HbA1c levels but highest third for hypoglycaemic events and change in body weight. Therefore, these alternative insulin-based options were recommended in specific circumstances such as where an individual may be at increased risk of hypoglycaemia.
145	Non Reg SH	Article published in the Lancet	General	General	General	The revised draft guidelines represent a missed opportunity for NICE and remain of questionable utility. Primary care doctors and nurses, in particular, are struggling to look after growing numbers of patients with T2DM. These healthcare professionals need clear, sensible guidance, based on evidence (and cost), but most importantly on safety.	Thank you for your feedback. The recommendations in the guideline are based on clinical effectiveness reviews which incorporate safety outcomes and evidence from *de novo* health economic modelling. This evidence was interpreted by the clinical experience of the guideline development group.
146	Non Reg SH	Article published in the Lancet	General	General	General	We strongly recommend that in further revisions to the NICE guideline: 1) repaglinide is withdrawn as a first-line agent; 2) the prominence given to sulphonylureas at all stages of intensification is reduced; 3) the BMI restrictions and stopping rules for GLP-1RAs are redrawn; 4) the SGLT-2 inhibitors are fully included; 5) individualized care for insulin management should mean just that, rather than restricting choice on cost; and finally 6) the promotion of "waiting for failure" approach is reviewed.	Thank you for your feedback. 1) Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based

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							combinations for drug intensification. 2) The guideline development group (GDG) disagrees that sulfonylureas in particular are prominently placed in the recommendations and algorithm. It is unclear how sulfonylureas can be less prominent at intensification phases without complete removal. However, the treatment options have been re-ordered alphabetically. 3) Given the evaluated clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 on GLP-1 mimetics (GLP-1s) have been retained. 4) Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. NICE is also exploring different ways of presenting this information. 5) Individualised care does not preclude guidance on clinically and cost-effective treatment options. 6) The GDG disagrees that the guideline promotes clinical inertia. Within the

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							guideline, regular review with reinforcement of diet, lifestyle and adherence to treatment is recommended, along with consideration to stop ineffective medicines. The GDG also recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals appropriate target and intensification HbA1c levels.
147	Non Reg SH	Article published in the Lancet	General	General	General	**References** 1. NICE. Type 2 diabetes: guideline consultation https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0612. Accessed June 2015. 2. Barnett AH. NICE draft type 2 guidelines: a cause for concern. *Lancet Diabetes Endocrinol* 2015; **3**: 403-5. http://dx.doi.org/10.1016/s2213-8587(15)00053-4 3. Khurrem S, Ali Yasin M, Asrar A, Qamar S. Comparison of repaglinide in the reduction of HbA1C of type 2 diabetic patients. http://pjmhsonline.com/comparison_of_repaglinide_with_g.htm. Accessed 15 July 2015.	Thank you for the references.

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						4. Hussain Shah Z, Saleem K, Mahboob F, Jibran R. A comparative study of repaglinide in type 2 diabetic patients. http://pjmhsonline.com/JulySept2011/a_comparative_study_of_repaglini.htm. Accessed 15 July 2015. 5. Fang FS, Gong YP, Li CL, *et al*. (2014) Comparison of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus. Eur J Endocrinol 2014; **170**: 901-8. 6. Actos Tablets. Summary of product characteristics. https://www.medicines.org.uk/emc/medicine/4236. Accessed 21 July 2015. 7. Altaf QA, Barnett AH, Tahrani AA. Novel therapeutics for type 2 diabetes: insulin resistance. *Diabetes Obes Metab* 2015; **17**: 319-34. 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* 2014; **14**: 52-9. http://dx.doi.org/10.15277/bjdvd.2014.015 9. Care Quality Commission. Regulation 20: duty of candour, March 2015. Available from: http://www.cqc.org.uk/sites/default/files/20150327_duty_of_candour_guidance_final.pdf. Accessed 20 July 2015. 10. Monami M, Marchionni N, Mannucci E. Long-	

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						acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2008; **81**: 184-9.	
148	Non Reg SH	Article published in the Lancet	General	General	General	**Conflict of interest** Dr JP O'Hare: Reader in Medicine Warwick Medical School and Hon Consultant Physician and Director of Community Diabetes Services UHCW/Coventry and Rugby. Duality of interests: lectures and advisory honoraria (Sanofi and Novo Nordisk). Dr D Miller-Jones: Chairman Primary Care Diabetes Society, UK and Ireland; Associate Specialist in Diabetes, Royal Gwent Hospital and GP with a special interest in diabetes. Duality of interests: Novo Nordisk, AstraZeneca, Janssen, Takeda, Lilly, MSD, Sanofi. Dr W Hanif: University Hospital Birmingham, UK. Duality of interests: Chair, South Asian Health Foundation; research and travel grants and consultancy fees from Novo Nordisk, Sanofi, AstraZeneca, Merck and Boehringer Ingelheim Allianz. D Hicks: Nurse Consultant, Diabetes for Barnet, Enfield and Haringey Mental Health Trust; Co-chair of Training Research and	Thank you for your feedback.

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						Education for Nurses on Diabetes (TREND). Duality of interests: Worked with Novo Nordisk, Lilly, AstraZeneca, MSD, Abbott, Janssen, Roche and BD on advisory boards and provided presentations at conferences sponsored by the pharmaceutical industry. Dr D Leslie: Professor of Diabetes and Autoimmunity, Queen Mary, University of London, and Consultant Physician, St Bartholomews Hospital, London. Duality of interests: Advisory Boards for Novo-Nordisk, GSK, Diamyd, Hyperion (no funding conflict of interest). Professor SC Bain: Professor of Medicine (Diabetes), Swansea, UK. Duality of interests: Abbott, AstraZeneca/BMS, Boehringer Ingelheim, Eli Lily, GSK, MSD, Janssen, Novartis, Novo Nordisk, Sanofi, Takeda, Servier, Roche, Pfizer. Professor AH Barnett: Emeritus Professor of Medicine, University of Birmingham and Consultant Physician, Heart of England NHS Foundation Trust, Birmingham, UK. Duality of interests: honoraria and lecture fees from AstraZeneca, MSD, Boehringer	

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						Ingelheim, Takeda, Novartis, Janssen, Eli Lilly, Sanofi, Novo Nordisk.	
1	SH	GP update / Red Whale	General	General	General	This looks MUCH more sensible! I can both do this in clinical practice and teach it! I still think a table of the common side effects, contraindications, impact on weight gain, risk of hypos, use in renal/liver impairments, long term safety profile (and state if not yet known) and costs would be really useful to help clinicians which of the various options listed are sensible for the patient before me. And I note the changes for gastroparesis, although I would still be concerned about using metoclopramide for this indication. It isn't precisely covered by the MHRA guidance but they do talk about not using for prolonged periods (in the context of dyspepsia).	Thank you for your feedback. The suggestion of a patient decision aid has been passed on to NICE implementation team. The accompanying footnote for metoclopramide states "Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2013) notes that metoclopramide has well-known risks of neurological effects such as short-term extrapyramidal disorders and tardive dyskinesia. It advises that metoclopramide should be prescribed only for short-term use (up to 5 days) at a maximum dose of 30 mg in 24 hours (usual dose of 10 mg up to 3 times a day)."
5	SH	Royal College of Pathologists	General	General	General	No comments.	Thank you for your feedback.
6	SH	Royal College of Surgeons	General	General	General	No comments.	Thank you for your feedback.
41	SH	Primary Care Diabetes Society	General	General	General	The PCDS would like to thank and acknowledge the efforts that have been put into this draft Document by NICE. There has been significant improvement in the revision. For a guideline to be useful, it needs to fulfil several criteria:- • Be clear and easy to follow by both	Thank you for your feedback. The recommendations in this guideline are based on evaluations of current clinical (including short and long-term safety concerns) and cost-effectiveness evidence, up to a search cut-off date. Following the

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						specialists and non specialists • Reflect a Prudent health principle ;- • Look at the acquisition costs of therapies and balance these against effectiveness • Consider compliance of therapies by patients • Include the increased costs for monitoring / screening • Review the risks imposed by therapies both in the short term (Hypoglycaemia , weight gain) and the longterm (cardiovascular risk and benefits) • Be current so that all latest evidence and new therapies are included • Emphasis conflicts that may be present :- Setting targets for individual patients Highlighting risks that certain therapies may cause to aid decision choices • Help pro-active management by offering suggestions regarding when to consider intensifying therapy as well as what to move onto inorder to reduce inertia in clinical care • To be comparable or an improvement on pre –existing guidelines. Despite the changes that have been made by the guideline committee, it is still felt that not all these criteria have been reached. We would strongly advised further revision of the guidelines before	first consultation, the guideline development group (GDG) considered the stakeholders' feedback on the appropriateness and implementability of the blood glucose management recommendations and associated algorithms. While taking into account the evidence base, these recommendations and algorithms were 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 guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. It is unclear which aspects of the list the current guideline does not cover. Analyses undertaken in the guideline and associated

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						publication.	deliberations of the guideline development group are recorded in the 'Linking evidence to recommendations' tables in the full guideline in which consideration has been given to the issues outlined in the criteria list..
64	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	General	General	General	ABCD welcomes the improvements to the first draft of the guideline, and appreciates the GDG's responses to its comments.	Thank you for your feedback.
88	SH	AstraZeneca	General	General	General	AstraZeneca is pleased to see NICE has recognised the weight of stakeholder opinion and substantially revised its guidance on the pharmacological management of blood glucose since the release of the first draft. Further, we appreciate NICE's positive response to requests from the clinical community that a further consultation on a revised draft be undertaken: we welcome the opportunity to respond. AstraZeneca recognises that there have been many improvements to the guideline: for example, the revised draft provides for greater flexibility and will help ensure that pharmacological interventions are offered on an individualised basis. However, we believe that the draft does not go far enough in support of an individualised	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. Newer and more innovative medicines that are not included in guidelines can be evaluated in the NICE technology appraisal process. 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 relevant technology appraisals.

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						approach to patient care. The final guidelines should allow clinicians flexibility to tailor treatment choices to the individual patient; and to prescribe newer, more innovative, medicines where clinically appropriate.	
107	SH	Department of Health	General	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.
135	SH	Janssen	General	General	General	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 whilst an improvement from the previous version, still 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 clinical community as well as the Department of Health (DH) Constitution strongly support that therapeutic decisions should be made coordinated around and tailored to patient preference; giving patients the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Janssen, therefore, welcomes the recommendation made by NICE within the CG	Thank you for your feedback. The recommendations in this guideline are based on evaluations of current clinical (including short and long-term safety concerns) and cost-effectiveness evidence of licensed medicines and combinations outlined in the scope. Newer and more innovative medicines that are not included in guidelines can be evaluated in the NICE technology appraisal process. 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 relevant technology appraisals. It is expected that clinicians would discuss the benefits and risks of each treatment options with individuals before deciding the

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						supporting the adoption of an individualised approach to diabetes care. For consistency throughout the guideline, Janssen would therefore suggest for a second time that NICE also consider adding the phrase 'Patient preference following discussion of benefits and harms' to be applicable at each decision point throughout the pharmacotherapy treatment algorithm as well as highlight it at the top of the pharmacotherapy treatment algorithm. Moreover, seemingly misaligned with the recommendation that patients' target HbA1c level should be set on an individual basis and achieved with low hypoglycaemic-risk medicines to maintain the highest standards of patient safety (recommendation 1.3.4.1), later recommendations and the pharmacotherapy treatment algorithm appear rather prescriptive as to which target levels to aim for and with which medicines depending purely on the patients' stage of disease, discounting an individuals' potential predispositions and pre-exiting complications. Janssen, recommend that the prescriptive targets set in the pharmacotherapy treatment algorithm and recommendations are removed or at the very least relaxed to a preferred target range. Importantly, the DH Constitution as well as the 5-year forward view also stipulates that the NHS is	appropriate course of action at each decision point. Given that the algorithm has been simplified to a single A4 document, it is not feasible to repeat this information at every decision point. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels. Individualised care does not preclude guidance on clinically and cost-effective treatment options. The antihyperglycaemic pharmacotherapy recommendations and algorithm were derived following consideration of the clinical and cost-effectiveness evidence and guideline development group's clinical experience. The cost-effectiveness analyses considered long-term outcomes and costs achieved via HbA1c control as

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						committed to providing best value for taxpayers' money and the most effective, fair and sustainable use of finite resources proposing the redesign of payments systems to reward quality. Thus, Janssen suggests that the pharmacotherapy treatment algorithm should not have a focus on in-year cost saving through recommending lowest acquisition cost medicine but rather more consider long-term outcomes achievable through initial tight yet safe glycaemic and multi-morbidity control. Additionally, the DH Constitution encourages the use of all nationally approved treatments, drugs and programmes that have been recommended by NICE for use in the NHS. The 5-year forward view represents the shared view of the NHS' national leadership, and 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. Similarly, the Innovation Health and Wealth agenda aims to accelerate the adoption of new Innovation. 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,	well as short-term outcomes and drug costs (see appendix F). Recommendations referring to drug cost were made when drugs were found to have sufficiently similar clinical and cost-effectiveness. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. As aforementioned, NICE anticipates that the majority of healthcare professionals will access the guidance via the NICE website and the NICE pathways tool. NICE is also exploring different ways of presenting this information. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the GDG agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high

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						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 within the flow of the algorithm and not simply within a footnotes. Lastly, Action for Diabetes 2012 in their state of the nation report emphasised the importance of primary care in managing the disease. Whilst improvement has been made with the pharmacotherapy treatment algorithm; Janssen would like to highlight that limiting the initiation of GLP-1 agonist therapy to specialist care, 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.	volume of referrals even if there were no accredited GPs in the multidisciplinary team.
136	SH	Janssen	General	General	General	**Reference List:** Dias et al (2014) NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework For Pairwise And Network Meta-Analysis Of Randomised Controlled Trials. Accessed: 24th July 2015. Available at: http://www.nicedsu.org.uk/TSD2%20General%20	Thank you for the references.

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						meta%20analysis%20corrected%2015April2014.pdf Deed et al (2012) Aust Fam Physician. Early and tight glycaemic control, the key to managing type 2 diabetes. 41(9):681-684. Handelsman, (2015) AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY – CLINICAL PRACTICE GUIDELINES FOR DEVELOPING A DIABETES MELLITUS COMPREHENSIVE CARE PLAN – 2015. Endocrine practice Vol 21 (Suppl 1) Hoaglin et al (2011) Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. Value in Health. 14: 429–437. Inzucchi, et al 2015 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.	

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						Jansen et al (2011) Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value in Health. 14: 417-428.	
159	SH	Lilly UK	General	General	General	Thank you for the opportunity to comment on the second consultation draft of the NICE type 2 diabetes guideline. We welcome the changes that have been made to the first draft, especially those which addressed some of the points we raised during the first consultation e.g. clarifying the term 'specialist care setting' and simplifying the algorithm. However, we are concerned that a number of our comments did not result in any changes. As a result we would like to reiterate our previous comments on the recommendations for the use of glucagon like peptide-1 receptor agonists (GLP-1 RAs).	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority

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							groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the GDG agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary

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							team.
164	SH	Merck Serono	General	General	General	Merck Serono is appreciative of NICE's approach to the consultation of the initial draft of the Adult Type 2 diabetes guidance and welcomes the reintroduction of Metformin MR as an option for patients who cannot tolerate standard release metformin. Merck Serono has no further comments to make on this guidance.	Thank you for your feedback.
168	SH	Merck Sharp & Dohme UK	General	General	General	**Transparency of evidence considered for pharmacological therapy** The NICE guidelines manual 2012 states that "recommendations should contain enough information to be understood without reference to the evidence or other supporting material"[1]; however, this is not the case when recommendations have been made for a DPP-4 inhibitor in the short guideline document and treatment algorithm (page 23). In the interest of patient centred care and to maintain the rigor associated with NICE clinical guidelines, MSD ask for consistency and transparency between the full and short guideline documents. In the short guideline, HCPs should have access to information on which molecules where included in the review when prescribing a class intervention i.e. DPP-4 inhibitors, and GLP-1s. This is currently stated in Table 42 in the full guideline (page 169), but the information is not	Thank you for your feedback. The rationale for the dipeptidyl peptidase-4 (DPP-4) inhibitor class recommendations is provided in the 'Linking evidence to recommendations' tables in the full guideline (see sections 8.4.7, 8.4.11 and 8.4.15) and outlined here. When defining the decision problem for the antihyperglycaemic pharmacological question, the guideline development group (GDG) preferred not to make an *a priori* assumption of class effect across DPP-4 inhibitors. Therefore, each individual option for which evidence was available was analysed separately. Having reviewed the assembled evidence for each phase of treatment, the GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could, in fact, be considered interchangeable: • In a few areas, a case could be made for

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						available in the current second draft version of the short guideline, including the treatment algorithm. This will ensure that HCPs have all the required information to make appropriate prescribing decisions when using the guidelines and will avoid misinterpretation of the recommendations. For example, the current text would suggest that evidence for all the interventions within the DPP-4 inhibitor class were considered by the GDG. However, this is not the case and an assumption of a class effect has been applied; this is not clearly documented in the short guideline. The existing T2DM guideline (CG87 2009) states the interventions considered when recommending a class of drugs. For example, at first intensification the current 2009 CG87 states "Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin…[2]. MSD would also welcome this level of transparency in the new guideline. <u>Proposed amendments to the short version of the clinical guideline</u>: **Initial drug treatment** **Section 1.6.23** Offer standard-release metformin as the initial drug treatment for adults	the superiority of 1 option over another (for example, at initial therapy, sitagliptin seemed to have somewhat superior benefits to vildagliptin at similar net costs). • In other areas, all the DPP-4 inhibitors for which evidence was available appeared to have very similar benefits, harms and costs (for example, in combination with metformin at first intensification). • Elsewhere in the treatment pathway, evidence was extremely limited (for example, sitagliptin–metformin–sulfonylurea was the only treatment combination for which evidence was available at second intensification) or absent (for example, at first intensification, there was no evidence that could be used to assess the relative clinical effectiveness and cost effectiveness of DPP-4 inhibitors in combination with pioglitazone or sulfonylureas). Having considered these different situations, the GDG concluded that the most helpful recommendations would be ones that treated DPP-4 inhibitors as a class. Had it been presented with evidence that suggested that 1 or more of the options was superior to others across all phases of treatment, the GDG would clearly have been inclined to favour such option(s) in its

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						In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with: • **a dipeptidyl peptidase-4 (DPP-4) inhibitor (linagliptin, saxagliptin, sitagliptin, vildagliptin) or** • pioglitazone **or** • repaglinide **or** • sulfonylurea **First intensification of drug treatment** **Section 1.6.24** In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with: • **metformin and a DPP-4 inhibitor (linagliptin, saxagliptin, sitagliptin, and vildagliptin) or** • metformin and pioglitazone **or** • metformin and a sulfonylurea **Treatment algorithm (Page 23 of 52)** When a DPP-4 inhibitor is recommended this should be footnoted to state: **"The GDG considered the evidence for 4 of the 5 DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin, and vildagliptin)".**	recommendations. However, the picture that had emerged was much more sporadic, and the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. Moreover, the GDG was mindful that a series of recommendations that alternated between treating DPP-4 inhibitors as a class, in some parts of the treatment pathway, and focusing on individual options in others would be confusing to readers of the guideline, even if those recommendations could be directly allied with the available evidence. For all of these reasons and to allow flexibility in selecting individual options in clinical practice, the GDG took the view that recommendations should consistently refer to DPP-4 inhibitors as a class. The following sentence has been added to the blood glucose pharmacotherapy section in the NICE short version and algorithm for greater clarity: "Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP 1) mimetics and sulfonylureas refer to each of these groups of drugs at a class level."

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						(Highlighted text indicates addition/ alteration) References 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 7 July 2015 2. NICE CG87, Type 2 diabetes: The management of type 2 diabetes. May 2009. https://www.nice.org.uk/guidance/cg8 7; accessed July 2015	
170	SH	Merck Sharp & Dohme UK	General	General	General	**TECOS** MSD acknowledge the feedback received from the GDG in relation to TECOS (Trial Evaluating Cardiovascular Outcomes for Sitagliptin), and fully appreciate that this study falls outside the scope of this guideline. However, MSD ask that the GDG consider the results of TECOS as an exceptional circumstance. The results of TECOS, a cardiovascular safety study, provides evidence that address not only a call to research from NICE (Draft guideline 1st consultation), but also data relevant to patient safety. TECOS enrolled patients with T2DM and a history of cardiovascular disease, and were treated long-term (median follow-up of 3 years) with sitagliptin in addition to usual care (n=7,332) or placebo in	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. Moreover, based on the information provided in the feedback and full publication, TECOS does not meet the inclusion criteria as a proportion or all patients were taking pre-existing oral antidiabetic drugs/insulin (confounding) and comparisons are likely to be across treatment phases.

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						addition to usual care (n=7,339). The primary endpoint was a composite cardiovascular endpoint (time to the first cardiovascular-related death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina requiring hospitalisation). In the primary analysis of the primary outcome in the per-protocol population, sitagliptin was found to be non-inferior to placebo demonstrating no increased risk for major cardiovascular events as defined by the primary endpoint when sitagliptin is added to usual care compared with placebo plus usual care (hazard ratio 0.98 (95% CI: 0.88 to 1.09, p<0.001), non-inferiority margin pre-specified as 1.30)[1]; this was supported when analysed in the intention-to-treat population. Unlike previous findings, reported in other cardiovascular safety trials with other DPP-4 inhibitors, there was no increased risk for hospitalisation due to heart failure when sitagliptin was added to usual care compared with placebo plus usual care (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98)[1]. There are four potential explanations for the results reported in TECOS, including; intrinsic pharmacological differences between the DPP-4 inhibitors, variation in background care between studies, difference in the recording and definition of heart-failure events, or simply chance. The authors concluded that among patients with type 2 diabetes and established cardiovascular disease, the addition	

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						of sitagliptin to usual care did not have a significant effect on the rates of major adverse cardiovascular events or hospitalisation for heart failure[1]. Reference 1. Green JB, Bethel A, Armstrong PW et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232-42	
195	SH	NHS England	General	General	General	*1.6.28* Indications for initiation of GLP-1 agonists are still somewhat restrictive. Furthermore, 1.6.28 "Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (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)." - This could more appropriately read "or", rather than "and".	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with

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							due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
196	SH	NHS England	General	General	General	*1.4.8* 1.4.8 still recommending simultaneous commencement of 2 anti-hypertensive agents as first line for hypertensive Africans and Caribbean's, which is not what we tend to do clinically - most clinicians would introduce one at a time, in which case, the guideline should be recommending which comes first (if ACE inhibitor, there can be a recommendation to raise awareness that introduction of an additional second line agent may be required quite quickly).	Thank you for your feedback and useful suggestion. It was not within the scope of the guideline at this update to consider hypertension. This topic has been flagged to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.
197	SH	NHS England	General	General	General	I would still suggest taking out repaglinide from the guideline altogether. Very few UK clinicians	Thank you for your feedback. Based on the evaluated evidence, for people who are

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						will have any experience using it at all, and the fact that it is only licensed as mono therapy or in combination with metformin means that further escalation necessitates discontinuation, which is unnecessarily cumbersome.	contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
210	SH	Royal College of Nursing	General	General	General	The Royal College of Nursing welcomes the opportunity to comment of the second consultation on the pharmacological management of blood glucose in adults with type 2 diabetes. The RCN invited members who care for people with diabetes to review the draft document on its behalf. The comments below are based on feedback from our members.	Thank you for your feedback.
211	SH	Royal College of Nursing	General	General	General	Our members consider that the draft guideline on 'blood glucose management' pf type 2 diabetes is better and far more in keeping with clinical practice; offering all of the groups of agents at each intensification step. Our members are also pleased to note that expressions such as 'choose the option with the lowest acquisition cost' have been removed from the guidelines.	Thank you for your feedback.
21	SH	Royal	General	General	General	Our members are pleased to see in particular that	Thank you for your feedback.

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2		College of Nursing				the Dipeptidyl peptidase-4 (DPP4), inhibitors have now been given the same weighting as the other oral drugs mentioned. They consider this a huge relief, particularly for some of their patients who are very vulnerable to hypoglycaemia.	
213	SH	Royal College of Nursing	General	General	General	Our members have also commented that it seems a shame that the SGLT-2 drugs are referred to only briefly in the management of type 2 diabetes and only by a link to another document. They commented that they have used SGLT-2 drugs on patients who struggle to control blood glucose levels with goods results. The drugs have also been beneficial to some patients who do not tolerate Metformin and have reacted to other drugs. They consider that it would be helpful to have clear guidelines about the use of SGLT-2 drugs particularly for the group of patients that they apply to.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
297	SH	South Asian Health Foundation	General	General	General	In general the guideline is an improvement from the last one. The tables are still confusing. The role and place of SGLT-2 inhibitors in treatment pathway is not elucidated properly although these are covered by a separate TAG it will be important to incorporate them with the main guidelines as this would lead to confusion especially in the primary care. The importance given to Repaglinide is not justified by any evidence and in a south Asian context they will be difficulties around compliance	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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

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						with thrice a day dosing and fasting during religious periods.	diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
298	SH	South Asian Health Foundation	General	General	General	The algorithm for GLP 1RA BMI recommendation "adjust accordingly for people from black, Asian and other minority ethnic groups" should be changed to "BMI >27.5 for black, Asian and other minority ethnic groups"	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher

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							(and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG agreed that, given the clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Reference to the 2013 published NICE public health guidance (PH46) on "Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK" is made available in section 3.2 of the NICE short version.
260	SH	Takeda UK Ltd	General	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,	Thank you for your feedback.

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						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. We are pleased that since the first draft released for consultation in January 2015, there have been a number of amends to the draft guideline, which have addressed the majority of questions we raised in response to the first consultation. In general, Takeda support the main recommendations of the guideline. Takeda UK Ltd are pleased that the guidelines provide a variety of options to the prescriber for patients 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.	
261	SH	Takeda UK Ltd	General	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 guideline publication of June 2014. However, since the scope was issued, Takeda UK Ltd have launched the DPP-4 inhibitor alogliptin in the UK (January 2014) and the guideline	Thank you for your 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

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						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. (Please also see comment below.) As alogliptin has been available in the UK since January 2014, with the majority of data published before this, we would still welcome a more comprehensive review of the evidence for alogliptin that has been published to date, including the alogliptin EXAMINE study within the context of other outcomes studies for antidiabetic agents that have reported in recent years. Conversely, we understand the time constraints and subsequent delay this would impose on 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	were excluded as comparisons were across treatment strategies (see Appendix L rows 588 and 761). The information provided will be passed to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.

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						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** 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 (including with metformin and a sulphonylurea) or with insulin. The safety and efficacy of alogliptin when used as	

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						triple therapy with metformin and a sulphonylurea have not been fully established. Caution should be exercised when alogliptin is used in combination with metformin and a thiazolidinedione as an increased risk of hypoglycaemia has been observed with this triple therapy. In case of hypoglycaemia, a lower dose of the thiazolidinedione or metformin may be considered. Alogliptin has not been studied in combination with sodium glucose cotransporter 2 (SGLT-2) inhibitors or glucagon like peptide 1 (GLP-1) analogues. **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] This study was fully published online in Diabetes, Metabolism and Obesity in September 2014 and in print in December 2014. • Alogliptin provides similar HbA1c reductions in older (≥65 years) and younger patients (<65	

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						years) with no differences seen in the safety profile[12] **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]	

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						• 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 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] – Patients were followed up to 40 months (median of 18 months). • 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]	

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						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 **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	

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						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 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	

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						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. • 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]	
4	SH	GP Update / Red Whale	Full	General	General	Maybe I have missed it but in the first draft I thought you said not to use modified release	Thank you for your feedback. The guideline development group (GDG) noted that there

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						metformin and sulphonylureas. You now specify a place for MR metformin (if standard release is not tolerate) but I can't now see any reference to MR sulphonylureas. Is it worth including a recommendation on this? (apologies if I have missed this)	was limited evidence on alternative forms of metformin for people who cannot tolerate standard-release metformin. The GDG agreed that the additional cardiovascular benefits associated with metformin use warranted a trial of modified-release metformin and based on clinical experience, a trial of modified-release metformin should be considered as an alternative for people who are unable to tolerate standard-release metformin because of gastrointestinal side effects, as occurs in standard practice. The GDG noted that there was even less evidence (2 trials) available for modified-release sulfonylurea which did not show it to be better than alternative options. The GDG noted that the main advantage of modified-release sulfonylurea was the need to take fewer tables but agreed that there were alternative drugs within the sulfonylurea class that could be administered once a day. The GDG agreed that given the greater cost associated with modified-release sulfonylurea and lack of evidence, this option could not be recommended.
56	SH	British Medical Association	Full	General	General	We believe that the revised guideline reflects some of the comments made not only by the BMA but also by the Association of British Clinical Diabetologists, and we welcome the attention paid	Thank you for your feedback

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						to these comments.	
57	SH	British Medical Association	Full	General	General	We were pleased to see that Repaglinide is no longer the first choice for treatment of type 2 Diabetes	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
58	SH	British Medical Association	Full	General	General	We believe that there are not adequate resources within primary care to implement this guideline. This places GPs in a position of potential medicolegal jeopardy over which they have no control. We believe that NICE guidance should always recognise the limitation under which NHS professionals have to work and produce guidance which is deliverable within these constraints.	Thank you for your feedback. NICE do take into account implementation issues throughout the development of guidance through the support of stakeholders, the expertise of the guideline development group and the work of the implementation team at NICE. While NICE recognise implementation of guidance may generate new challenges, NICE provides evidence-based guidance which must seek to tackle variation in practice and influence the highest quality care.
75	SH	Association of the British Pharmaceuti	Full	General	General	The Association of the British Pharmaceutical Industry (ABPI) would like to thank the guideline development group (GDG) for a second	Thank you for your feedback

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		cal Industry				opportunity to respond to the draft NICE Type 2 diabetes guidelines. The overwhelming response from stakeholders, including the ABPI, illustrates how important this guideline is to the complexities of managing people living with type 2 diabetes.	
76	SH	Association of the British Pharmaceuti cal Industry	Full	General	General	On 7 January 2015, the National Institute for Health and Care Excellence (NICE) issued a draft clinical practice guideline on the management of type 2 diabetes by the NHS in England and Wales. The ABPI agreed 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 patients' quality of life. However, we shared the concerns of the diabetes community that the section on 'Blood Glucose Management' was fundamentally flawed. On 21 April 2015 NICE acknowledged that it had received extensive responses from registered stakeholders and had made substantial changes to the draft recommendations. On 26 June 2015 NICE opened a second consultation on recommendations for the pharmacological management of blood glucose in adults with type 2 diabetes.	Thank you for your feedback
77	SH	Association of the British Pharmaceuti cal Industry	Full	General	General	The ABPI acknowledges that there have been many welcome improvements to the draft guideline. However the ABPI believes that the draft guideline is still missing the opportunity to	Thank you for your feedback. Following the first consultation, the guideline development group (GDG) considered the stakeholders' feedback on the

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						support an individualised approach to treating diabetes.	appropriateness and implementability of the blood glucose management recommendations and associated algorithms. While taking into account the evidence base, these recommendations and algorithms were simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Individualised care does not preclude guidance on clinically and cost-effective treatment options.
78	SH	Association of the British Pharmaceutical Industry	Full	General	General	The ABPI believes that the draft guideline is still too heavily focused on achieving short-term cost efficiencies, at the expense of individualised patient care and potentially long term outcomes and complications. It appears 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.	Thank you for your feedback. The antihyperglycaemic pharmacotherapy recommendations and algorithm were derived following consideration of the clinical and cost-effectiveness evidence and guideline development group's clinical experience. The cost-effectiveness analyses considered long-term outcomes and costs achieved via HbA1c control as well as short-term outcomes and drug costs (see appendix F). Recommendations referring to drug cost were made when drugs were found to have sufficiently similar clinical and cost-effectiveness. Individualised care does not preclude guidance on clinically and cost-effective treatment options that promotes informed

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							decisions based on the best available evidence.
79	SH	Association of the British Pharmaceutical Industry	Full	General	General	Given the commitments from NHS England to support the uptake of innovation, we find it concerning that the draft guideline maintains drug costs as a criterion. NICE should focus on delivering guidance that promotes the highest standards of care; ensuring appropriate access to the latest cost-effective treatments is an important factor in achieving that. Furthermore, the PPRS agreement presents the 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 to best suit patients medical needs, because the costs of prescribing branded medicines over agreed growth levels are underwritten by the pharmaceutical industry.	Thank you for your feedback. The antihyperglycaemic pharmacotherapy recommendations and algorithm were derived following consideration of the clinical and cost-effectiveness evidence and guideline development group's clinical experience. The cost effectiveness considered long-term outcomes and costs achieved via HbA1c control as well as short-term outcomes and drug costs (see appendix F). Recommendations referring to drug cost were made when drugs were found to have sufficiently similar clinical and cost-effectiveness. Individualised care does not preclude guidance on clinically and cost-effective treatment options that promotes informed decisions based on the best available evidence. Newer and more innovative medicines that are not included in guidelines can be evaluated in the NICE technology appraisal process. 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

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							relevant technology appraisals.
80	SH	Association of the British Pharmaceutical Industry	Full	General	General	We believe there are important changes still needed. The proposed treatment algorithm still does not reflect NICE's current Single Technology Appraisals guidance nor does it evaluate the newer diabetes medicines that have not been through NICE TA review. The draft guideline continues to fall short of the high standard set by the well-established and respected joint guideline 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. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring further ways of presenting this information. The pharmacological blood glucose lowering therapies review included drug classes and specific drugs as listed in the guideline scope, for example, acarbose, sulfonylureas. 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

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							recommendations was to provide specific guidance on optimal treatment options and/or combinations. The guideline development group (GDG) was clear that heterogeneous prescribing practice – especially at later stages of the treatment pathway – is commonly driven by prescriber habit, rather than true differences in clinical circumstances. For this reason, the GDG wanted to provide more specific guidance for healthcare professionals to support improved prescribing practices. 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. Individualised care does not preclude guidance on clinically and cost-effective treatment options.
81	SH	Association of the British Pharmaceutical Industry	Full	General	General	The ABPI calls on NICE to ensure that the final guidelines fully support an individualised patient treatment approach in type 2 diabetes and that the treatment algorithm is closely scrutinized and tested to ensure it provides clear, consistent direction and does not cause confusion amongst healthcare professionals.	Thank you for your feedback. The guideline development group (GDG) has considered the issues raised by stakeholders at the second consultation, particularly with respect to the pharmacological management of blood glucose and have made further amendments to the algorithm and recommendations to facilitate evidence-based guidance that is user-

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							friendly to a wide range of stakeholders including non-specialists. Following the first consultation, the GDG considered the stakeholders' feedback on the appropriateness and implementability of the blood glucose management recommendations and associated algorithms. While taking into account the evidence base, these recommendations and algorithms were simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. Individualised care does not preclude guidance on clinically and cost-effective treatment options.
91	SH	AstraZeneca	Full	General	General	**<u>Potential for confusion regarding the position of insulin</u>** **Concern** Insulin is positioned in the second intensification box as an alternative to triple oral therapy, where as there is confusion as to the position of GLP-1 RAs (see comment 3). The draft guideline acknowledges that patients are often unwilling to start insulin because of fear of hypoglycaemia and potential impact on weight. Furthermore, it acknowledges that certain non-	Thank you for your feedback. In the metformin pathway, at second intensification, the following are available options: triple oral therapy (metformin+DPP-4 inhibitor+sulfonylurea or metformin+pioglitazone+sulfonylurea) and insulin-based treatments. Specific information on when the GLP-1 mimetics triple therapy combination becomes an option is provided in the recommendations and algorithm (see NICE short version): 1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation

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						insulin based drug combinations are associated with fewer hypoglycaemic events and, in some instances, weight loss *[page 251 full guideline]*. **Recommendation** Present insulin as an option in the second intensification box specifically for patients for whom a "triple non-insulin therapy..." (whether this be triple oral therapy or treatment with a regimen including a GLP-1 RA) "...is not effective, not tolerated or contraindicated".	1.6.27) is not effective, tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: • have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity, or • have a BMI lower than 35 kg/m^2 and: - for whom insulin therapy would have significant occupational implications, or - weight loss would benefit other significant obesity-related comorbidities. [new 2015]
101	SH	Central Manchester University Hospitals NHSFT	Full	General	General	Patient involvement in treatment decisions - most patients do not like to take drugs that cause weight gain or increase risk of hypoglycaemia. We feel that some separation of weight neutral/loss from weight gaining drugs may be helpful with pointing clinicians to choose these classes where appropriate. We feel that a summary table of drug class, effect on weight, hypoglycaemia risk, and cost ratio would be helpful.	Thank you for your feedback. The suggestion of a patient decision aid has been passed on to NICE implementation team.
102	SH	Central Manchester University Hospitals NHSFT	Full	General	General	Patient involvement in decisions – patient decision tools, such as similar to those for statins use and anticoagulation in AF could be helpful in aiding patient consultations	Thank you for your feedback. The comment has been passed on to the NICE implementation team.

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184	SH	North Central London Joint Formulary Committee	Full	General	General	Please ensure sub-bullets '○' are indented from main bullets '●' (eg. page 21, line 9 and 10 should be indented further)	Thank you for your feedback. The algorithm has been amended.
194	SH	NHS Choices	Full	General	General	The Digital Assessment Service welcome this guidance and have no comments on it as part of the consultation.	Thank you for your feedback
201	SH	NHS Havering Clinical Commissioning Group	Full	General	General	There is no mention of macular oedema being a contra indication for pioglitazone.	Thank you for your feedback. According to the summary of product characteristics **(**SPC), macular oedema is not a contraindication for pioglitazone, but rather a potential side effect.
215	SH	Royal College of Physicians of Edinburgh	Full	General	General	NICE does not give sufficient consideration to treatment combinations with insulin. Combining different classes of treatment is important in type 2 diabetes as they each target different physiological aspects of the disease. In clinical practice and according to NICE's own STAs, the use of oral therapies in combination with insulin can help many patients gain better control of HbA1c and lose weight, as well as reduce the amount of insulin required. However, in the draft guideline, the only medications that are highlighted as potential combination treatments with insulin are GLP-1 receptor agonists. SGLT2 inhibitors are also associated with better control of HbA1c and weight loss, as well as reduction in the amount of insulin required, and should be included.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations have been made. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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

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							between recommendations on type 2 diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information.
216	SH	Royal College of Physicians of Edinburgh	Full	General	General	GLP-1 receptor agonists and SGLT2 inhibitors are excluded from the first intensification stage. In line with the ADA/EASD guideline, it is important to ensure that clinicians have the flexibility to prescribe medicines for type 2 diabetes according to the individual needs of their patients. Although the draft guideline recognises this, it restricts the treatment options that are available at the first intensification stage by excluding GLP-1 receptor agonists and SGLT2 inhibitors. These are important treatment combination options, particularly for patients with high BMI and/or specific psychological or other medical problems associated with obesity and who are not able to take other treatments which are weight neutral/positive.	Thank you for your feedback. For the metformin pathway at first intensification, the guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective (as their higher incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains) and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where

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							GLP-1s would become an option. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification (including with insulin). 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
289	SH	Swansea NHS Trust	Full	General	General	*1.3.4.1* The guideline speaks to individualised HbA1c targets and yet uses the following phrases repeatedly: "In adults with type 2 diabetes, if HbA1c levels are not adequately controlled …….and rise to 58 mmol/mol (7.5%)" "agree a target and aim for an HbA1c level of 53 mmol/mol (7.0%). [new 2015]" We believe that the 'individualisation' of HBA1c means that continually referring to a level of 53 mmol/mol (7.0%) is both confusing and	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.

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						inappropriate. This also applies to the level of 58 mmol/mol (7.5%), which is the level for therapy escalation throughout the guideline. In our view, for elderly patients and those with cardiovascular (CV) and other co-morbidities, these levels are too LOW. This is acknowledged on page 18, line 37 onwards (reference to age, co-morbidities etc.), but how many busy general practitioners are likely to read the full text of this 345 page document (a rhetorical question with an answer close to zero). On the contrary, these HbA1c levels are inappropriately high for younger people with type 2 diabetes (T2DM) where setting an HbA1c level of 58 mmol/mol (7.5%) for intervention is institutionalising the treatment escalation inertia which is already widespread in the UK (and documented to be the worst in Western Europe)	Recommendations 1.6.7 and 1.6.8 (NICE short version) have been re-worded to emphasise the importance of supporting individuals in their HbA1c levels: 1.6.7 For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). **[new 2015]** 1.6.8 In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher: • reinforce advice about diet, lifestyle and adherence to drug treatment and • support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) and • intensify drug treatment. **[new 2015]**
290	SH	Swansea NHS Trust	Full	General	General	*1.3.4.2* The opportunity to use self-monitoring of blood glucose (SMBG) in younger patients as an educational tool is not recognised.	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None

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							of 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. Therefore, the guideline development group (GDG) made a strong "Do not routinely offer" recommendation for SMBG. The GDG did not review the evidence on the application of SMBG as an educational tool in younger people and therefore was not confident in making a specific recommendation in the absence of evidence.
291	SH	Swansea NHS Trust	Full	General	General	*1.3.5 line 15 onwards* The continued inclusion of repaglinide is inappropriate for metformin-intolerant patients, given it's licenced indications. This appears to be a reluctance of NICE to admit error in the 1st draft of this guidance, rather than a decision based on clinical evidence or advice.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based

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							combinations for drug intensification.
292	SH	Swansea NHS Trust	Full	General	General	*1.4 Algorithm* We believe that the algorithm in the full 2nd draft guideline (1.4, page 14) is crucial since it is a single page document, which is likely to be laminated and widely used in those practices which follow the up-dated NICE guidance. We think there are many flaws in this algorithm as it currently stands: a) <u>In the 'Metformin: First intensification' section:</u> Add-on to metformin is illogical and inconsistent with that in the main text 1.3.5 (line 17): *Pioglitazone – no hypoglycaemia but weight gain* is listed first *SU – hypoglycaemia and weight gain* is listed second *Gliptin – no hypoglycaemia and no weight gain* is listed third However, in the 'Metformin: contraindicated or not tolerated' section, listing of alternative first-line therapies is consistent with the text (and logical); DPP-4s, pioglitazone & SU. How can this be justified? b) Why is there no triple therapy option for metformin-pioglitazone-gliptin in the 'Metformin: First intensification' section? c) GLP-1RA use has been relegated further down the algorithm than previously. Currently in NICE CG 87 it is a 3rd-line option; this draft only sanctions GLP-1RA triple after failure of triple oral	Thank you for your feedback. a) The order of the treatment options was originally based on the evaluated clinical and cost-effectiveness evidence. However, the treatment options have now been re-ordered alphabetically. Given concerns over the safety of pioglitazone, a footnote on the safety alerts was added following the first consultation, with a note to exercise particular caution if the person is at high risk of the adverse effects of this drug. b) The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. c and d) This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had

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						therapy i.e. it is now a fourth-line therapy. d) Why in a 'blood glucose lowering therapy' guideline, which to this point has ignored weight, have a BMI cut-off for initiation of GLP-1RA (35 Kg/m2) and a 3% weight loss stopping rule for GLP-1RAs? It is illogical and inconsistent. e) In the 'Metformin: contraindicated or not tolerated' section i. Repaglinide should not be included here since further intensification would not be 'intensification', it would be a switch (and, therefore, a recommendation for treatment inertia). ii. First intensification – why name dual combinations? Simply say add one of the unused alternatives. This can be done if repaglinide is excluded from the previous list. iii. Why are SGLT-2s not specifically mentioned in this pathway? iv. Why are GLP-1RAs apparently excluded in this pathway?	better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack

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							of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. e i) Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification. e ii) For consistency and clarity, formatting in first intensification for the non-metformin pathway is the same as the metformin pathway. e iii) Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification (including insulin options). NICE anticipates that the

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							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 the technology appraisals. NICE is also exploring different ways of presenting this information. e iv) There were no relevant studies examining non-metformin based GLP-1 treatment combinations identified (cut off search date of June 2014) and therefore the GDG was not confident in making a specific recommendation in the absence of evidence.
293	SH	Swansea NHS Trust	Full	General	General	*1.4 Algorithm* General comment. There can be no excuse for relegating the SGLT-2 inhibitor class to a footnote of the 1.4 algorithm, with no mention in the guideline text. This class of oral anti-diabetic drug has been licenced within Europe for two-and-a-half years and should be fully integrated into any modern guidance.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of

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							presenting this information.
294	SH	Swansea NHS Trust	Full	General	General	General comment. Given the huge amount of effort that NICE has put into previous analyses of individual drugs in both guidelines and single technology assessments (STAs), it seems odd that these are being ignored, so as to allow newer (cheaper) agents to have equivalent status. An example of this is alogliptin in the DDP-4 class where, in Wales, it is not recommended by the All-Wales Medicines Strategy Group for triple therapy use, but this is not made clear by this NICE guidance.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. The rationale for the dipeptidyl peptidase-4 (DPP-4) inhibitor class recommendations is provided in the 'Linking evidence to recommendations' tables in the full guideline (see sections 8.4.7, 8.4.11 and 8.4.15) and outlined here. When defining the decision problem for the antihyperglycaemic pharmacological question, the guideline development group (GDG) preferred not to make an *a priori* assumption of class effect across DPP-4 inhibitors. Therefore, each individual option for which evidence was available was analysed separately. Having reviewed the assembled evidence for each phase of

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							treatment, the GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could, in fact, be considered interchangeable: • In a few areas, a case could be made for the superiority of 1 option over another (for example, at initial therapy, sitagliptin seemed to have somewhat superior benefits to vildagliptin at similar net costs). • In other areas, all the DPP-4 inhibitors for which evidence was available appeared to have very similar benefits, harms and costs (for example, in combination with metformin at first intensification). • Elsewhere in the treatment pathway, evidence was extremely limited (for example, sitagliptin–metformin–sulfonylurea was the only treatment combination for which evidence was available at second intensification) or absent (for example, at first intensification, there was no evidence that could be used to assess the relative clinical effectiveness and cost effectiveness of DPP-4 inhibitors in combination with pioglitazone or sulfonylureas). Having considered these different situations, the GDG concluded that the most helpful

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							recommendations would be ones that treated DPP-4 inhibitors as a class. Had it been presented with evidence that suggested that 1 or more of the options was superior to others across all phases of treatment, the GDG would clearly have been inclined to favour such option(s) in its recommendations. However, the picture that had emerged was much more sporadic, and the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. Moreover, the GDG was mindful that a series of recommendations that alternated between treating DPP-4 inhibitors as a class, in some parts of the treatment pathway, and focusing on individual options in others would be confusing to readers of the guideline, even if those recommendations could be directly allied with the available evidence. For all of these reasons and to allow flexibility in selecting individual options in clinical practice, the GDG took the view that recommendations should consistently refer to DPP-4 inhibitors as a class. The following sentence has been added to the blood glucose pharmacotherapy section in the NICE short version and algorithm for greater clarity: "Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1

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							(GLP 1) mimetics and sulfonylureas refer to each of these groups of drugs at a class level."
295	SH	Swansea NHS Trust	Full	General	General	General comment. The regulatory authorities require massive (and phenomenally expensive) CV safety studies for all new diabetes medicines and yet NICE choses to completely ignore these data. Again, the best example is from the DDP-4 class, where heart failure as a safety signal emerged from a study of saxagliptin (with a non-significant trend seen with alogliptin) – both of these results available during the period of the original guideline development. The reassuring data from the sitagliptin TECOS study (albeit after the guideline time-limits) could easily be included for reassurance of prescribers.	Thank you for your feedback. Long-term drug safety (including cardiovascular outcomes) 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. The TECOS study does not meet the inclusion criteria as a proportion or all patients were taking pre-existing oral antidiabetic drugs/insulin (confounding) and comparisons are likely to be across treatment phases. As stated in the 'Linking evidence to recommendations' table (section 8.5.4, full guideline), the guideline development group (GDG) noted that the Medicines and Healthcare products Regulatory Agency (MHRA) whose specific remit is to examine the benefits and harms of pharmacological interventions and issue regulatory action when necessary, considers all available evidence such as those from databases and registries and therefore is able to provide the most up-to-date information in this area.
296	SH	Swansea NHS Trust	Full	General	General	General comment. There is a recommendation for early use of insulin	Thank you for your feedback. In order to ensure patient safety, it is anticipated that healthcare professionals prescribing insulin

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						in this draft guideline but despite a 345 page document, the recommendations for how this should be initiated and (more importantly) up-titrated is minimal. The comment in 8.4.17.6 "*For guidance on insulin delivery for adults with type 2 diabetes, see the insulin 24 delivery section in the NICE guideline on type 1 diabetes. [new 2015]"* is surely inadequate since few (if any) people with type 1 diabetes should be receiving basal-only or fixed mixture insulin preparations, whilst these account for the majority of insulin prescribing in T2DM.	should be competently trained in dosing and titration.
265	SH	Takeda UK Ltd	Full	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.	Thank you for the references.

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						9. Pratley RE, *et al. Diabetes* 2012; 61 (Suppl 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	

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						Information Centre. All rights reserved OGL 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. Lewis JD et al. *JAMA* 2015;314(3):265-277. doi:10.1001/jama.2015.7996.	
288	SH	University Hospital Birmingham NHSFT	Full	General	General	The guidelines are much better than the earlier version. Although four areas of concerns remain that can have a huge impact on diabetes management and outcomes: .1) The Hba1c target of 7.5% may be higher for young patients with complications where the target should be around 6.5%. 2) Repaglinide is still recommended as second line in the treatment algorithm based on weak evidence and network meta-analysis. Considering it is a three times daily drug with large dose variation compliance would be a big issue. 3) The BMI cut-off of 35 for GLP-1's are not based on any evidence. We feel they should be 30 for white Europeans and 27.5 for south Asians. 4) The SGLT-2 inhibitors have a separate HTA but non-inclusion of them in the treatment algorithm will cause confusion in the primary care.	Thank you for your feedback. 1) The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals appropriate target and intensification HbA1c levels. 2) Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone

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							and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification. 3) The GDG noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with

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							due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Reference to the 2013 published NICE public health guidance (PH46) on "Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK" is made available in section 3.2 of the NICE short version. 4) Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. NICE

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							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 the technology appraisals. NICE is also exploring different ways of presenting this information.
59	SH	British Medical Association	Full	12	General	1.2.1 We believe that the recommendation about structured education does not take into account the resources available. In many areas there is a considerable waiting list for the Structured Education Programmes and therefore locally these are reserved for those who have poor control and who it can benefit the most. In certain patients, if good control of blood sugars, lipids and blood pressure are achieved by advice from the general practitioner or practice nurse then the Educational Programmes could be reserved for those who have poor control, if there are capacity issues.	Thank you for your feedback. NICE do take into account implementation issues throughout the development of guidance through the support of stakeholders, the expertise of the guideline development group and the work of the implementation team at NICE. While NICE recognise implementation of guidance may generate new challenges, NICE provides evidence-based guidance which must seek to tackle variation in practice and influence the highest quality care. As stated in section 4.1.4 in the full guideline, well-designed and well-implemented programmes are likely to be effective and cost-effective interventions for people with type 2 diabetes. In addition, for those people in whom education delivered in a group setting is appropriate, it is evidently likely to be more cost effective. GPs have an important role in delivering

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							structured education.
228	SH	South East Strategic Clinical Network	Full	12	35	We would value the inclusion of recommended targets for people who are 'functionally dependent' as stated in International Diabetes Federation's 2013 *Managing Older People with Type 2 diabetes.* They recommend 53-64mmol/mol. Sub category A: frail < 70mmol/mol, Subcategory B: dementia < 70mmol/mol. This is important in reducing harm to elderly people with limited life expectancy who are unlikely to benefit from tight glycaemic control but are at real and increasing risk of complications of glucose lowering therapies, particularly hypoglycaemia.	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). Evidence specifically in subgroups of the elderly i.e. frail or those with dementia was not identified. The GDG considered recommendation 1.6.9 which provides guidance on circumstances when target HbA1c levels should be relaxed to be adequate in facilitating discussion with individuals to set appropriate target and intensification HbA1c levels.
229	SH	South East Strategic Clinical Network	Full	12	37	This recommendation suggests waiting until levels go beyond 58mmol/mol (7.5%) before intensifying treatment on from a single drug. This is likely to lead to clinical inertia which is a well known cause of avoidable glycaemic burden. It contradicts your statement page 12, line 35 as you are not taking into account individual patient criteria. This is displayed so well in figure 1 of the ADA/EASD position statement: *Management of hyperglycaemia in Type 2 diabetes, 2012 and the updated version in* 2015. Would it be possible to refer to this diagram in the NICE guidelines to	Thank you for your feedback. The guideline development group (GDG) disagrees that the guideline promotes clinical inertia. Within the guideline, regular review with reinforcement of diet, lifestyle and adherence to treatment is recommended, along with consideration to stop ineffective medicines. The GDG also recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised

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						portray a consistent message and back up your original statement?	care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals appropriate target and intensification HbA1c levels.
282	SH	UK Clinical Pharmacy Association	Full	13	3	1.3.4.2 – It is a backwards step to take out the need for blood glucose testing with concomitant steroids for patients with diabetes. We feel it was important to consider this for short term use, as it is a recognised reason for admission to hospital when left unchecked. This statement around steroids is buried in the central text separate from the initial recommendations (page 19, line 26). This recommendation also doesn't appear in the algorithm in the top text.	Thank you for your feedback. The recommendation has been retained (see recommendation 1.6.14 in the NICE short version): 1.6.14 Consider short-term self-monitoring of blood glucose levels in adults with type 2 diabetes (and review treatment as necessary): • when starting treatment with oral or intravenous corticosteroids, or • to confirm suspected hypoglycaemia. [new 2015] Page 13, rec 1.3.4.2 (full guideline) highlights the Key Priorities for Implementation (KPIs). The guideline development group agreed that it would be helpful to restrict information in the KPIs and algorithm that are common in clinical practice.
209	SH	Royal College of General	Full	13	4	The conditions outlined do require self monitoring but the decision as to whether self monitoring of blood glucose is appropriate for other adults with	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no

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		Practitioners				Type 2 diabetes should be based on an individual assessment as per the Diabetes UK paper position statement in April 2013.	SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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. Therefore, the guideline development group (GDG) made a strong "Do not routinely offer" recommendation for SMBG. However, the GDG provided circumstances when SMBG should be considered. It is expected that clinicians would discuss the benefits and risks of SMBG with individuals before deciding the appropriate course of action.
198	SH	NHS Havering Clinical Commissioning Group	Full	13	8	After …risk of hypoglycaemia include (in particular sulphonylureas and post prandial regulators, consider patients on dual therapy and chronic kidney disease)	Thank you for your feedback. The guideline development group (GDG) considered that the wording in recommendation 1.6.13 (NICE short version) adequate in providing guidance on the circumstances when self-monitoring of blood glucose (SMBG) should be considered. It is expected that clinicians would discuss the benefits and risks of SMBG with individuals before deciding the appropriate course of action.
23	SH	South East	Full	13	13	This is not in line with revised algorithm. There is	Thank you for your feedback. Ten Key

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0		Strategic Clinical Network				no mention of modified-release Metformin	Priorities for Implementation (KPIs) were selected by the guideline development group, one of which is recommendation 1.6.19 (NICE short version): 1.6.19 Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. [new 2015] Subsequent recommendations on gradually increasing the dose of standard-release metformin (1.6.20) or using modified-release metformin in the event of intolerance (1.6.21) were not prioritised to be added to the list of KPIs.
247	SH	South Sefton Clinical Comissioning Group	Full	13	15	Should it not read "if standard release or modified release metformin is contra-indicated or not tolerated…" so that it concurs with the algorithm on page 14.	Thank you for your feedback. 'Metformin' is used in other recommendations following recommendation 1.6.19 and 1.6.21 (NICE short version) to refer to both standard-release and modified-release for brevity.
183	SH	North Central London Joint Formulary Committee	Full	14	1 -2	It is disappointing that NICE has not built the SGLT-2 advice into the algorithm. We acknowledge that footnotes refer to TA228, 315 & 336. In the same regard, please add TA203 & 248 (GLP-1RAs) for completion.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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

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							diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version).
264	SH	Takeda UK Ltd	Full	14 20	1 1-11	Takeda are pleased that the recommendation to "*Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the 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)"* has been added for all treatment options. This allows for individualised therapy, whilst minimising prescribing costs.	Thank you for your feedback.
263	SH	Takeda UK Ltd	Full	14 257	2 26	Takeda is confident in the therapeutic benefits of pioglitazone and its importance as a treatment for T2DM, when used according to current Summary of Product Characteristics (SmPC) recommendations. We are pleased that key additional safety information has been added to the guideline recommendations and algorithm. With regards to pioglitazone and the risks of bladder cancer, two Kaiser Permanente Northern California (KPNC) studies have recently been	Thank you for your feedback and reference to the recent JAMA publication. 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. Assessment of the JAMA paper indicates that the cohort study does not meet the inclusion criteria as a proportion or all patients were on unknown background medications.

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						published in The Journal of American Medical Association (JAMA)[22] "Pioglitazone Use and Risk of Bladder Cancer and Other Common Cancers in Persons with Diabetes" James D. Lewis, MD, MSCE; Laurel A. Habel, PhD; Charles P. Quesenberry, PhD; Brian L. Strom, MD, MPH; Tiffany Peng, MA; Monique M. Hedderson, PhD; Samantha F. Ehrlich, PhD; Ronac Mamtani, MD, MSCE;Warren Bilker, PhD; David J. Vaughn, MD; Lisa Nessel, MSS, MLSP; Stephen K. Van Den Eeden, PhD; Assiamira Ferrara, MD, PhD The paper presents the final results of two prospective observational studies on pioglitazone performed on KPNC data base: • A 10 year observational prospective study looking at the Pioglitazone exposition and the potential risk of bladder cancer. It is a cohort and nested case-control analyses among persons with diabetes. The cohort followed 193 099 persons aged 40 years or older in 1997-2002 until December 2012; 464 case patients and 464 matched controls were surveyed about additional confounders. • A long term prospective observational study	

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						looking at the exposition of pioglitazone and the potential risk of 10 most common cancer except bladder cancer. The cohort included 236 507 persons aged 40 years or older in 1997-2005 and followed until June 2012. The conclusion of the paper is: *Pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded. The increased prostate and pancreatic cancer risks associated with ever use of pioglitazone merit further investigation to assess whether they are causal or are due to chance, residual confounding, or reverse causality.*	
2	SH	GP Update / Red Whale	Full	14	General	For each of your suggested intensifications you advise to aim for a target of 53/7 AFTER intensification EXCEPT for those in whom metformin is contraindicated/not tolerated when you suggest a target of 48 for those on monotherapy with a gliptin or pio and 53 for those on repaglinide and SU. I appreciate that the latter induce hypos whereas this is rare with gliptins/pio but WHY the tighter target (tighter than any other step) in those on gliptin/pio? Can you explain your rationale please? (and if there isn't a good rationale please can you abandon this idiosyncratic suggestion – it	Thank you for your feedback. To promote patient safety, the guideline development group (GDG) considered it important to relax the HbA1c target levels for individuals on drugs (repaglinide and sulfonylureas) that are associated with an increased risk of hypoglycaemia, compared to those on drugs without an associated increased risk (dipeptidyl peptidase-4 [DPP-4] inhibitors and pioglitazone).

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						just makes things more complicated)	
3	SH	GP Update / Red Whale	Full	14	General	Why are the gliflozins just added as a footnote? Why are they not included in your algorithm of drugs? Also do note the MHRA Drug Safety Update on diabetic ketoacidosis in people with T2DM on gliflozins at relatively low blood sugars (June 2015)	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. With regard to the recent Medicines and Healthcare products Regulatory Agency (MHRA)'s safety alert on SGLT2s, given that the current guideline is cross-referring to NICE technology appraisals, it is anticipated that this information would be included in the technology appraisal guidance.
40	SH	Aneurin Bevan University Health Board	Full	14	General	The guideline seems to advise that for type 2 diabetics, after life style interventions, if HbA1C rises >6.5% metformin is offered if the patient can tolerate it and there is no contraindication. The target for HbA1C is at 6.5%. For patients who cannot tolerate metformin or if it is contra-indicated for it, a few drugs are offered,	Thank you for your feedback. To promote patient safety, the guideline development group (GDG) considered it important to relax the HbA1c target levels for individuals on drugs (repaglinide and sulfonylureas) that are associated with an increased risk of hypoglycaemia, compared to those on

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						consider DPP4i, pioglitazone, replaglinide or SU. But I do not understand the rationale as to why there are two HbA1C targets, 6.5% for patients on DPP4i or pioglitazone. However, for patients who are on repaglinide or SU the target of HbA1c is higher at 7%. If one considers that HbA1C targets have prognostic significance, then why should one group of patients who for no fault of their own, are prescribed repaglinide or a SU should be more relaxed and have a higher target of 7%. I suspect it has something to do with the higher risks of hypoglycaemia in the repaglinide and SU group. But it still does not make sense in terms of patients outcome. Bearing in mind that most of the oral hypoglycaemics can only reduce the HbA1C by the average of 0.8%, this further highlight that there should not be a difference in HbA1C targets in patient groups of 0.5%. I think that the target should be the same for all groups and is set at 6.5%. The algorithm suggests that for patients of the first intensification and second intensification stages, the HbA1C target should be more relaxed and set at 7%. I agree with that. In fact, for elderly patients, those over 70, I have no problem to set the target at 7.5%.	drugs without an associated increased risk (dipeptidyl peptidase-4 [DPP-4] inhibitors and pioglitazone). The GDG recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.
214	SH	Royal College of	Full	14	General	The proposed treatment algorithm is not completely aligned with other NICE guidance and	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on

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		Physicians of Edinburgh				could lead to clinician confusion and sub-optimal patient care. The use of SGLT2 inhibitors has now been incorporated into the algorithm, but only in the footnotes. We would suggest that SGLT2 inhibitors are listed alongside the other choices of medication in both first and second intensification, to ensure consistency with the NICE Single Technology Appraisals (STAs) for SGLT2 inhibitors. Secondly, the position of GLP-1 receptor agonists at the second intensification stage is far from clear.	sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment

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							costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective as indicated in the recommendations and algorithm.
218	SH	Royal Pharmaceutical Society	Full	14	General	This algorithm is a vast improvement on the first version of this guideline. However, it is still unclear as to where some therapies sit within it. Certain medicines, such as the SGLT2 drugs, are mentioned in the footnote that they have NICE Technology Appraisal status and they will be reviewed. However, it would be more helpful and improve use of the algorithm, if those medicines in the footnote that have TAs are actually integrated into the algorithm where they should sit (as dual / triple therapies). If this does not happen there is the potential for a large volume of duplication across England once these guidelines are launched as local areas produce a local algorithm based on the national standard but including all potential drug pathways.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
23	SH	South East	Full	14	General	1.4	Thank you for your feedback. Cross-referral

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1		Strategic Clinical Network				We are keen to encourage the use the NICE algorithm for blood glucose lowering therapy as a prescribing guide and as a training resource. In its current state the algorithm is out of date before it is published. The omission of SGLT-2 inhibitors. SGLT-2 inhibitors are included on the NICE pathway for Blood Glucose Lowering therapies for Type 2 diabetes, so inclusion in the algorithm would maintain a consistent, up-to-date approach	to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
248	SH	South Sefton Clinical Comissioning Group	Full	14	General	For intensification where a sulfonylurea is advised in conjunction with metformin should repaglinide be suggested as an alternative to an SU if patients encounter problems with hypoglycaemia as it can be beneficial for a select group of patients.	Thank you for your feedback. No relevant evidence was identified (cut off search date: June 2014) that included metformin and repaglinide treatment combination. Therefore, the guideline development group was not confident in making a specific recommendation in the absence of evidence.
283	SH	UK Clinical Pharmacy Association	Full	14	General	1.4 – This algorithm is better but very wordy and requires a high level of understanding. There are still a number of anomalies. With GLP-1's this is going to overwrite previous NICE TA for liraglutide – is this guidance stating that 1.8mg of liraglutide is now considered cost effective by NICE? SGLT2 inhibitors and their role are still not mentioned – can the recommendations from the relevant TAGs please be added, as this will	Thank you for your feedback. The algorithm is a pictorial representation of the recommendations. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level. The guideline

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						provide prescribers with a 'one-stop' reference document rather than expecting prescribers to cross-reference multiple sources. We do not expect the recommendations to be reviewed, just included. The technology appraisals allow SGLT2 inhibitors to be placed as a second line alternative and we cannot see the problem with including them in the algorithm – even if they are not discussed in detail. There is limited mention of particularly significant adverse effects e.g. pancreatitis, issues with pioglitazone and DKA with SGLT2s. There should be a section on what is significant and relevant for decision making. We were pleased to see the amendment to insulin and GLP-1 on specialist advice rather than previously described as specialist only. Repaglinide is still recommended despite its unusability in clinical practice (can only be combined with metformin). We would urge that this recommendation is removed.	development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1s had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. No clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. NICE anticipates that the

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							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 the technology appraisals. NICE is also exploring different ways of presenting this information. The suggestion of a patient decision aid has been passed on to NICE implementation team. Following the second consultation, some stakeholders expressed concerns regarding the specialist care advice term. Because of the lack of evidence and that GLP-1s in combination with insulin are normally prescribed in complex cases, the GDG agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no

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							accredited GPs in the multidisciplinary team. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
82	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* **Specific clinical concerns** The ABPI welcomes the equal positioning of DPP-4is with pioglitazone and sulphonylureas in the new draft and the incorporation of SGLT2 inhibitors into the algorithm, but is disappointed to see that this is limited to a mention in the footnotes. We acknowledge that SGLT2 inhibitors were not included in the evidence review as part of the development of this guideline; however, in order to avoid confusion among healthcare professionals, we recommend that this guideline is adjusted to ensure consistency with the NICE	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of

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						Single Technology Appraisals (STAs) for SGLT2 inhibitors.	presenting this information.
83	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* The position of GLP-1 receptor agonists at the second intensification stage is open to interpretation and appears to be at odds with NICE's clinical positioning in its own STAs for this class of medicine. For example, it appears as though insulin is recommended as an alternative to triple oral therapy and that GLP-1 receptor agonists are recommended only when triple oral therapy is failing; however, the clinical positioning of GLP-1 receptor agonists in the STAs suggest their use before insulin. The ABPI would recommend that the draft guideline is adjusted to minimise any misunderstanding by healthcare professionals and further allow for an individualised approach to treating diabetes	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). In the metformin pathway, at second intensification, the following are available options: triple oral therapy (metformin+DPP-4 inhibitor+sulfonylurea or metformin+pioglitazone+sulfonylurea) and insulin-based treatments. Specific information on when the GLP-1 mimetics triple therapy combination becomes an option is provided in the recommendations and algorithm (see NICE short version): 1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation 1.6.27) is not effective, tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: • have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity, or

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							• have a BMI lower than 35 kg/m^2 and: - for whom insulin therapy would have significant occupational implications, or - weight loss would benefit other significant obesity-related comorbidities. [new 2015]
84	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* Combining different classes of treatment is clinically important in type 2 diabetes as they each target different physiological aspects of the disease. The algorithm does not give any consideration to the use of oral treatments in combination with insulin. For example, prescribing an SGLT2 inhibitor or DPP-4 inhibitor with insulin can improve glycaemic control, enable management of weight control, and alter the amount of insulin needed, without increasing the risk of hypoglycaemia. The ABPI requests that NICE ensures the information relating to treatment combinations with insulin is complete.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations have been made. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification (including insulin-based treatments).
85	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* The draft guidelines appear to undermine NICE's definition of individualised patient care by not reaching an appropriate clinical balance in respect of the GLP-1 stopping criteria. As they currently stand, they appear incompatible with targets for HBA1C and inappropriate for insulin patients. In the case of patients who are deriving significant clinical benefit from their treatment, it is critical that the stopping rules do not result an effective	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be

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						treatment being stopped unnecessarily.	significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.

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86	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* Different classes of type 2 diabetes medicines can have a variable effect on weight and risk of hypoglycaemia, so these are important elements for healthcare professionals to consider. The latest draft of the guideline includes a list of factors for medical professionals to consider when selecting a treatment for type 2 diabetes, but weight and hypoglycaemia risk are not explicitly included. This appears to be an oversight, as it is widely recognised that these factors can improve medical outcomes as well as patents' quality of life, self-esteem and treatment satisfaction.	Thank you for your feedback. The guideline development group (GDG) agreed that to facilitate usability, the list of factors should be concise and coherent. The GDG considered a range of adverse effects including weight and hypoglycaemia.
87	SH	Association of the British Pharmaceutical Industry	Full	14	General	*1.4* In line with the ADA/EASD guideline, it is important to ensure that clinicians have the flexibility to prescribe medicines for type 2 diabetes according to the individual needs of their patients. While the draft guideline recognises this, it continues to restrict the treatment options that are available at the first intensification stage by excluding GLP1 receptor agonists. This is an important treatment combination option, particularly for patients with high BMI and/or specific psychological or other medical problems associated with obesity and who are not able to take other treatments that are weight neutral/positive. The ABPI asks NICE to make this option available, in line with their objective of supporting an individualised approach to patient	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks

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						care in type 2 diabetes.	associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
176	SH	National Diabetes Nurse Consultant Group	Full	15	1	It would be helpful if specific targets for the frail, and those with additional co- morbidities could be stated. This is important as the over all target for HbA1c has now reverted back to 53 mmol/mol . The use of SUs and or insulin to reach this target may lead to hypoglycaemia in the certain patient groups such frail. Older people, end of life patients and those with impaired kidney disease - reference to IDF targets for the Frail elderly would be helpful here	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). Adequate evidence in subgroups of the elderly i.e. frail or end-of-life patients and those with specific comorbidities was not identified. The GDG considered recommendation 1.6.9 which provides guidance on circumstances when target HbA1c levels should be relaxed to be adequate in facilitating discussion with individuals to set appropriate target and

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							intensification HbA1c levels.
281	SH	Training, Research and Education for Nurses in Diabetes	Full	15	1	It would be helpful if specific targets for the frail, and those with additional co- morbidities could be stated. This is important as the overall target for HbA1c has now reverted back to 53 mmol/mol . The use of SUs and or insulin to reach this target may lead to hypoglycaemia in the certain patient groups such frail. Older people, end of life patients and those with impaired kidney disease	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). Adequate evidence in subgroups of the elderly i.e. frail or end-of-life patients and those with specific comorbidities was not identified. The GDG considered recommendation 1.6.9 which provides guidance on circumstances when target HbA1c levels should be relaxed to be adequate in facilitating discussion with individuals to set appropriate target and intensification HbA1c levels.
23	SH	Weight Watchers	Full	15	3	Weight Watchers is pleased to see the focus on individualised care. We would welcome additional emphasis on increased support upon diagnosis with education around the vast benefits of weight loss improving quality of life and reducing the risk of the long-term complications of the condition.	Thank you for your feedback. It was not within the scope of the guideline at this update to consider education at diagnosis. 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 has a guideline on the identification, assessment and management of obesity in adults and children which includes

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							recommendations on bariatric surgery, diet, physical activity and behavioural interventions to assist in weight loss.
244	SH	South East Strategic Clinical Network	Full	15	3	the guidance has not included any of the evidence available for patient activation (Judith Hibbard et al) and how essential this is in order to empower people to develop the knowledge, skills and confidence to self-manage and therefore truly achieve the known improved outcomes from collaborative care planning (RCGP Care Planning Document 2011) and a person centered approach. Clinician and Patient activation would impact on people's rates of healthy behaviour change and therefore engagement with weight loss, increased exercise, stopping smoking as well compliance with medication.	Thank you for your feedback. It was not within the scope of the guideline at this update to consider patient activation. 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.
245	SH	South East Strategic Clinical Network	Full	15	13	It is also important to recognise that structured education has to be flexible to people's needs in order for them to access it and improve the current appalling attendance rates ie group programmes outside of core working hours, on line, books etc.	Thank you for your feedback. It was not within the scope of the guideline at this update to consider structured education. However, NICE do take into account implementation issues throughout the development of guidance through the support of stakeholders, the expertise of the guideline development group and the work of the implementation team at NICE.
249	SH	South Sefton Clinical Comissioning Group	Full	17	44	For clarity does this mean do not prescribe aspirin for patients with microalbuminuria (i.e.Chronic Kidney Disease G—A2or3). There is the cohort of patients whose eGFR deteriorates with the addition or titration of an ACE inhibitor or ARB.	Thank you for your feedback. The guideline development group (GDG) discussed the use of antiplatelet therapy in people with microalbuminuria. Although the GDG recognised that microalbuminuria may be

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						This group may have atherosclerotic renal artery stenosis.	an indicator of cardiovascular risk because it may be an early signal of decline in kidney function, it also appears in people with type 2 diabetes and normal renal function. The GDG noted that evidence from the STENO 2 trial showed a reduction in cardiovascular disease and progression of renal disease in people with type 2 diabetes and microalbuminuria. However, the GDG noted that this study assessed a multifactorial intervention which included components that could all influence cardiovascular outcomes (that is, the use of aspirin [75 mg], renin–angiotensin system blockers and lipid-lowering agents and tight glucose regulation) compared with conventional therapy. Therefore the GDG was not certain that the findings could be robustly extrapolated to reflect the true effects of aspirin alone and did not consider it was appropriate to make a specific recommendation for a microalbuminuria subgroup. Based on the evaluated evidence, the GDG cannot recommend the use of aspirin specifically for patients with microalbuminuria.
250	SH	South Sefton Clinical Comissioning Group	Full	18	11	I believe that Fructosamine estimation is only available at a few laboratories in England and so is difficult to obtain.	Thank you for your feedback. The guideline development group (GDG) considered that only one of the 3 listed options in recommendation 1.6.3 (NICE short version)

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							is required. This represents a very small population, with the option to choose any of the 3 available methods.
181	SH	North Central London Joint Formulary Committee	Full	18	26 -29	This text clearly states "For adults with type 2 diabetes that is managed either by… a single drug that is not associated with hypoglycaemia, agree a target and aim for an HbA1c level of 48 mmol/mol (6.5%)". The treatment algorithm on pg. 14 states that "Agree a target and aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone or 53 mmol/mol (7.0%) for people on repaglinide or an SU". Please make the text on pg. 18 (line 26-29) reflect the advice in the algorithm.	Thank you for your feedback. The text in recommendation 1.6.7 (NICE short version) has been amended to: 1.6.7. For adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with one drug not associated with hypoglycaemia, support the person to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults on a drug associated with hypoglycaemia, support the person to aim for an HbA1c level of 53 mmol/mol (7.0%). [new 2015]
180	SH	North Central London Joint Formulary Committee	Full	18	30 -36	NICE specifies that a 'target' is different to a 'threshold for intensification'. Please provide advice on how to counsel patients that fall between these two values e.g. HbA1c >7.0% but <7.5%; a patient may feel that they are failing to reach their target however but no action is being taken by their healthcare providers.	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.

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							It is expected that healthcare professionals would explore reasons for missed target and support individuals, for example, reinforce lifestyle and dietary changes, provide structured education opportunities and advice on medicine adherence, as these measures may adequately improve HbA1c levels to delay or avoid drug intensification. HbA1c levels should be re-checked in 3 to 6 months as suggested for those who are not reaching 'target'. Increasing drug therapy remains an option if repeat tests indicate HbA1c levels are above target, but this should be considered in the light of risk of hypoglycaemia or other drug side effects.
251	SH	South Sefton Clinical Comissioning Group	Full	19	36	Including the use of in date quality control solution and how to obtain it, which is often overlooked.	Thank you for your feedback. The guideline development group considered that the use of in date quality control solution and methods of obtaining it are part of day-to-day practice.
232	SH	South East Strategic Clinical Network	Full	19	43	We are keen to encourage discussion about options available when considering treatment intensification. This requires NICE to include SGLT-2 inhibitors within the treatment algorithm.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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

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							area and should assure quick navigation between recommendations on type 2 diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information.
217	SH	Royal College of Physicians of Edinburgh	Full	19 256	General	Weight is not explicitly included as a factor to influence choice of treatment. The latest draft of the guideline includes a list of factors for medical professionals to consider when selecting a treatment for type 2 diabetes. Considering that 90% of people with type 2 diabetes are overweight, it is suggested that weight should be added to the list. Other parts of the guideline emphasise the importance of weight in type 2 diabetes and it is widely recognised that improved weight management can improve medical outcomes as well as a patient's quality of life, self-esteem and treatment satisfaction. Different classes of drugs used to treat type 2 diabetes can cause weight gain, weight loss or be weight neutral: so this is a very important element for healthcare professionals.	Thank you for your feedback. The guideline development group (GDG) agreed that to facilitate usability, the list of factors should be concise and coherent. The GDG considered a range of adverse effects including weight and hypoglycaemia.
233	SH	South East Strategic Clinical Network	Full	20	8	We are keen for healthcare professionals to take into account the individual's preferences and needs as one of the criteria when discussing treatment options. The current treatment algorithm is not taking into account a patient preference to lose weight or to avoid weight gain, This suggests a less than holistic approach to glucose lowering therapies and risks making the guidance out of	Thank you for your feedback. Following the first consultation, while taking into account the evidence base, the recommendations and algorithms were simplified and amended to place an increased emphasis on individualised care and choice around which pharmacological interventions are appropriate for consideration. The guideline

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						touch with clinical practice within an obesogenic environment particularly when one considers that the diabetes prevention programme will likely focus strongly on weight loss. The message received could be that weight control is only important if you don't have Type 2 diabetes once you have it weight gain is of little importance.	development group (GDG) 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. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. To facilitate this, a generic recommendation was 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)
252	SH	South Sefton Clinical Comissioning Group	Full	20	15	Carefully re-consider the diagnosis in case the patient in fact has Latent Autoimmune Diabetes of Adults, consider offering Ketostix until the diagnosis has been confirmed.	Thank you for your feedback. The guideline development group agreed that these patients would be identified in routine clinical follow-up and would not be treated differently.
182	SH	North Central London Joint Formulary Committee	Full	20	21 -23	Please provide the evidence summary that justifies the recommendation of metformin MR. If the recommendation for MR is based on expert opinion only (as documented on pg. 198) then this should be made clearer in the recommendations	Thank you for your feedback. The rationale for recommendation modified-release metformin is provided in section 8.4.7 (full guideline) and is outlined here. While the guideline development group (GDG) noted that there was limited evidence on

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							alternative forms of metformin for people who cannot tolerate standard-release metformin, the GDG agreed that based on clinical experience, a trial of modified-release metformin should be considered for people who are unable to tolerate standard-release metformin because of gastrointestinal side effects. The GDG agreed that the additional cardiovascular benefits associated with metformin use warranted a trial of modified-release metformin.
284	SH	UK Clinical Pharmacy Association	Full	20	30	*Page 20 lines 30-45, page 21 lines 1-12* **Recommendations 56 -59** –There no consistency, could drugs be listed alphabetically or state that this is the preferred order. Currently the list changes between sections which is confusing. Please add in recommendations from the NICE TAs on SGLT2's – stating when to use them	Thank you for your feedback. The order of the treatment options was originally based on the evaluated clinical and cost-effectiveness evidence. However, the treatment options have now been re-ordered alphabetically. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification (including insulin options). 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

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							the technology appraisals. NICE is also exploring different ways of presenting this information.
234	SH	South East Strategic Clinical Network	Full	20	33	If Pioglitazone is going to remain an option could the guidance state clearly a typical patient (male, high BMI, insulin resistant, abnormal lipid profile) who would benefit from Pioglitazone as well as a list of contraindications?	Thank you for your feedback. It is beyond the remit of the guideline to provide examples of typical patients. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: • heart failure or history of heart failure , • hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015]
235	SH	South East Strategic Clinical Network	Full	20	34	Repaglinide has been given equal weighting. We are concerned there is an increased safety risk including hypoglycaemia, confusion regarding dose titration for both the patient and healthcare professional, risk of use outside of it's license (failing to stop when adding a second drug (if Metformin is contraindicated) or a third drug. If Repaglinide is going to remain an option could the guidance clearly state a typical patient who would benefit from Repaglinide as well as the contraindications and when it should be stopped.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of

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							repaglinide, along with no available licensed non-metformin-based combinations for drug intensification. At dual therapy, a footnote highlights the need to introduce drugs in a stepwise manner, checking for tolerability and effectiveness of each drug. It is beyond the remit of the guideline to provide examples of typical patients.
236	SH	South East Strategic Clinical Network	Full	20	36 42	We would value SGLT-2 inhibitors being included at this point, in line with the technology appraisals 288,315 & 336 completed by NICE. The treatment pathway and NICE guidance are then offering a consistent message. We are concerned GLP-1 receptor agonists that are licensed, as dual therapy is not included here. Again it is not consistent with the NICE treatment pathway. An option would be to recommend as dual therapy with a higher BMI cut off point (i.e. 40)	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the recommendations and algorithm for use at first and second intensification. Due to automatic formatting of recommendations at the front of the full guideline, the SGLT-2 cross-referral has not appeared but does appear in the NICE short version and algorithm and within the full guideline (section 8.4.17). This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing

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							HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations.
253	SH	South Sefton Clinical Comissioning Group	Full	20	40	or repaglinide if episodes of hypoglycaemia and DPP4 and pioglitazone contra-indicated or not tolerated.	Thank you for your feedback. No relevant evidence was identified (cut off search date: June 2014) that included metformin and repaglinide treatment combination. Therefore, the guideline development group was not confident in making a specific recommendation in the absence of

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							evidence.
237	SH	South East Strategic Clinical Network	Full	21	4	We do not understand why GLP-1 receptor agonists are excluded from 59: line 4-11 and are listed separately. Insulin has been included on the list. Again this is inconsistent with the NICE Type 2 treatment pathway. It is also inconsistent with a holistic approach to glucose lowering therapy.	Thank you for your feedback. In the metformin pathway, at second intensification, the following are available options: triple oral therapy (metformin+DPP-4 inhibitor+sulfonylurea or metformin+pioglitazone+sulfonylurea) and insulin-based treatments. Specific information on when the GLP-1 mimetics triple therapy combination becomes an option is provided in the recommendations and algorithm (see NICE short version): 1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation 1.6.27) is not effective, tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who: • have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity, or • have a BMI lower than 35 kg/m^2 and: - for whom insulin therapy would have significant occupational implications, or - weight loss would benefit other significant obesity-related comorbidities. [new 2015] The guideline development group (GDG)

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							noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the

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							starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Individualised care does not preclude guidance on clinically and cost-effective treatment options.
199	SH	NHS Havering Clinical Commissioning Group	Full	21	9 10	It is felt that at second intensification sulphonylureas are no longer efficacious and should be replaced with SGLT2s as a consideration.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
238	SH	South East Strategic Clinical Network	Full	21	13	We don't agree with the recommendation of waiting for triple oral therapy to fail before considering GLP1 agents. They should be considered in certain groups of patients much earlier in the treatment pathway.	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while

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							triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be

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							changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. The GDG recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
285	SH	UK Clinical Pharmacy Association	Full	21 250	13 -33	**Recommendation 60 –** GLP-1 agonists were previously recommended as a first choice for triple therapy. This initiation has now been delayed until triple oral therapy has been tried first which is contradictory to the evidence. Given the current	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8

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						obesity crisis and the average primary care delay in reviewing medications (approx. 1 year) this seems a backwards step that will delay initiation of a very useful class. This therapy should be available for use as a first line choice in triple therapy if the criteria are met. This is supported by the commentary in Table 87 which acknowledged the benefits of weight loss using this combination. Triple oral therapy is only used because of a theoretical risk of hypo's and a perceived preference by patients. In addition the review of evidence section recognises that there is very little evidence for the combination of three oral agents, yet this is given higher preference order than the evidence based treatment of GLP1s in monotherapy and also in in dual therapy.	of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no

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							clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. The GDG recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option. GLP-1s are not licensed for monotherapy.
200	SH	NHS Havering	Full	21	1822	Consider waist circumference where BMI < 35 or in athletes where >35	Thank you for your feedback. The guideline development group (GDG) noted that while

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		Clinical Commissioning Group					triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. No clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
23	SH	South East	Full	21	18	We would value inclusion of a BMI level at which	Thank you for your feedback. The guideline

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9		Strategic Clinical Network			19	to consider GLP-1 Receptor Agonists for black, Asian and other ethnic minority groups	development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. No clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Reference to the

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							2013 published NICE public health guidance (PH46) on "Assessing body mass index and waist circumference thresholds for intervening to prevent ill health and premature death among adults from black, Asian and other minority ethnic groups in the UK" is made available in section 3.2 of the NICE short version.
240	SH	South East Strategic Clinical Network	Full	21	27	The ABCD Exenatide and Liraglutide audits highlighted trends in clinical practice whereby patients achieving one or other reduction (HbA1c or weight) remained on a GLP-1. Having gained such extensive observational data NICE have continued to promote discontinuation unless both HbA1c and weight reduction are reached. Can this be taken into account?	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach

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							to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
241	SH	South East Strategic Clinical Network	Full	21	27	It would be useful to have guidance if a patient has not met the criteria with one GLP-1 receptor agonist, can the healthcare professionals offer a second i.e. once weekly in place of a twice daily regimen or long-acting in place of a GLP-1 with a shorter half-life? This is a question often asked by primary care colleagues.	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1s had better

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							weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. No clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
242	SH	South East Strategic Clinical	Full	21	39	Within our SCN area East Kent has had experience in implementing a structured programme for starting insulin therapy, training	Thank you for your feedback on your experience of implementing a structured programme on insulin therapy.

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		Network				primary care healthcare professionals to support patients during the assessment, initiation and initial 6-months of insulin. The PITstop training course is already showcased on the NICE shared learning database.	
254	SH	South Sefton Clinical Comissioning Group	Full	21	General	Should reference be made to the NICE Guidelines relating to SGLT-2 inhibitors?	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the recommendations and algorithm for use at first and second intensification. Due to automatic formatting of recommendations at the front of the full guideline, the SGLT-2 cross-referral has not appeared but does appear in the NICE short version and algorithm and within the full guideline (section 8.4.17).
255	SH	South Sefton Clinical Comissioning Group	Full	21	General	For triple therapy containing Metformin would it be beneficial to suggest repaglinide as an alternative to sulfonylurea for a select group of patients who experience hypoglycaemic episodes ?	Thank you for your feedback. Repaglinide is not licensed for triple therapy.
256	SH	South Sefton Clinical Comissioning Group	Full	22	9	Is it worth stating the appropriate formulation of metformin should be continued….	Thank you for your feedback. Metformin is used in other recommendations following recommendation 1.6.19 and 1.6.21 (NICE short version) to refer to both standard-release and modified-release for brevity.
243	SH	South East Strategic Clinical	Full	22	10	The ADA/EASD 2012 & 2015 position statement recommends stopping SUs when prandial insulin is added. This is a clear message and may be of	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic

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		Network				benefit here. Again consistency across guidelines would be useful	modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations have been made. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. Recommendation 1.6.34 (NICE short version) highlights the importance of reviewing medications when starting insulin: 1.6.34 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. [new 2015]
185	SH	North Central London Joint Formulary Committee	Full	22	15 -24	The cost-effectiveness evaluation is noted in Appendix F. Please provide additional univariate sensitivity analyses for insulin glargine at 15% and 40% discount from list price to aid decision making. Biosimilar insulin glargine will shortly become available and prescribing is expected to shift from insulin glargine to biosimilar insulin glargine. Failure to do this will be to render this guideline out of date by Q4 2015 which would be very disappointing. Biosimilar insulin glargine is	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 (GDG) was that, on this occasion, any such further analysis would be of limited assistance to the GDG. Accordingly, the revision of the section on pharmacological management of

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						expected to be between 15-40% cheaper than insulin glargine. Please provide an additional univariate sensitivity analysis where insulin detemir's impact on weight is assumed to be equal to that for insulin glargine (justified as "The GDG expressed strong reservations as to whether these lower weight gains were seen in clinical practice and noted the very low quality of the clinical network supporting this evidence" pg. 252 in full guidance). Please provide a multivariate sensitivity analysis where insulin glargine is at 15% list price and insulin detemir's impact on weight is assumed to be equal to that for insulin glargine	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. A footnote on the use of biosimilars has been added to insulin glargine which states "The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication."
287	SH	UK Clinical Pharmacy Association	Full	22	General	There are lots of reference to insulin glargine. We presume this is the standard 100units/ml but there is no acknowledgement of the new 300units/ml preparation or the biosimilar preparation. This means that the insulin recommendations are already out of date and therefore do not provide helpful advice to prescribers who are choosing to use an analogue.	Thank you for your feedback. Specific dose recommendations have not been made for any antihyperglycaemic medicines. A footnote on the use of biosimilars has been added to insulin glargine which states "The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication."
202	SH	NHS Havering	Full	24	16	Assessment. Include every patient should have initial assessment of other causes of erectile	Thank you for your feedback. The guideline development group (GDG) has made minor

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		Clinical Commissioning Group				dysfunction? E.g. thyroid problems, low testosterone, B12/folic acid deficiencies, etc. phosphodiesterase-5 (PDE-5) inhibitors, are more effective if testosterone is at normal levels.	amendments to recommendation 1.7.14 (NICE short version): 1.7.14 **Assess, educate and support** men with type 2 diabetes who have problematic erectile dysfunction, addressing contributory factors such as cardiovascular disease as well as possible treatment options. [2015] The GDG agreed that "assessment" covers all the points raised in your feedback.
24	SH	Weight Watchers	Full	26	6	We recommend the consideration of SACN's report into Carbohydrates & Health into this evidence	Thank you for your feedback. It was not within the scope of the guideline at this update to consider diet/lifestyle 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.
25	SH	Weight Watchers	Full	26	General	We note little mention of diabetes prevention in this evidence. We would welcome the recommendation of diabetes prevention particularly for the benefit of family members of those diagnosed with type 2 diabetes who are likely to be at a high risk of developing the disease themselves.	Thank you for your feedback. This type 2 diabetes guideline does not cover prevention.
257	SH	South Sefton Clinical Comissioning Group	Full	26	General	Is it worth investigating the safety of metformin at a reduced dose for patients with an eGFR below 30?	Thank you for your feedback. A research recommendation has been added "In adults with type 2 diabetes and chronic kidney disease, what is the safety and

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							effectiveness of metformin?".
219	SH	Royal Pharmaceutical Society	Full	47	11	Individualised care needs to be better linked to currently available services such as Medicine Use Reviews and New Medicine Service provided by community pharmacists. These services can support individualised care and stopping inappropriate medicines.	Thank you for your feedback. This comment has been passed on to NICE implementation team.
220	SH	Royal Pharmaceutical Society	Full	47	25 -39	Pharmacists working in all sectors (community, hospital, GP practice, Care Homes and other primary care) will all input into the care and management of diabetic patients so must be included in any planned educational programmes. Particularly as they are the healthcare professional the patient is likely to interact with on a most frequent basis.	Thank you for your feedback. It was not within the scope of the guideline at this update to consider structured education.
221	SH	Royal Pharmaceutical Society	Full	122	38	Patients will need ongoing support and motivation so technologies should be utilised to ensure that all involved in care of the patient are aware of what the individual HbA1C target is. Healthcare professionals would also need to know when targets are changed along with the rationale for changing them	Thank you for your feedback. The comment has been passed on to NICE implementation team.
223	SH	Royal Pharmaceutical Society	Full	160	General	Treatment should be reviewed and patients should be reminded about what action to take when they are unwell. Community pharmacists are well placed to support and advise patients in these situations and also provide routine advice at the point of supplying new diabetic medicines or during MURs and NMS.	Thank you for your feedback. The guideline development group agrees and this information has been added to the 'Linking evidence to recommendations' table (see section 8.3.3 in the full guideline)
22	SH	Royal	Full	164	2	We welcome the further clarification of self-	Thank you for your feedback.

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2		Pharmaceutical Society			-27	monitoring of blood glucose although this may still be open to local interpretation and perhaps could be better aligned with DVLA recommendations.	Recommendation 1.6.12 (NICE short version) provides link to the DVLA guidance. 1.6.12 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. [new 2015]
258	SH	South Sefton Clinical Comissioning Group	Full	164	23	Including the use of in date quality control solution and how to obtain it, which is often overlooked	Thank you for your feedback. The guideline development group considered that the use of in date quality control solution and methods of obtaining it are part of day-to-day practice.
262	SH	Takeda UK Ltd	Full	167	15	As per the developers' response to our stakeholder comment on the previous consultation for this guideline, we would request to include that alogliptin is a treatment that was included within the search strategy. The developers' response to our comment to the previous consultation confirmed that "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."	Thank you for your feedback. This treatment was included within the search strategy (see Appendix C page 3). Studies after the cut off search date of June 2014 will be passed to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.

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187	SH	Newcastle University	Full	221	General	*8.4.10.1.4* Change in body weight text and interpretation: Part of the problem with the handling of DPP-4 inhibitors (which we strongly endorse as useful medications) relates to body weight change. This comes through strongest and most in error in this section, but is repeated several times in lesser form notably in the Evidence to recommendations sections on glucose-lowering agents. Here '8.4.10.1.4 Change in body weight' the words 'with a DPP-4 inhibitor (linagliptin) . . . were most effective at promoting weight loss at 12 and 24 months' occur. This is wholly inappropriate [and wrong]. None of the DPP4i SmPCs mention weight loss. This is because after adjustment for control arms the RCTs of the medications show weight neutrality taken together. The GDGs error (and now NICE's) appears to arise from the network analysis of around −2.5 kg (eg p 218 Fig 46), but that is a comparison netted against metformin-sulfonylurea – and sulfonylureas do cause about 2.5 kg weight gain averaged across RCTs in 12 months (and then no further change). Whether such a weight difference is worth ~£300 per year is for the GDGs judgement, but the correct justification is missing in all three categories where DPP-4i's are recommended alongside sulfonylureas.	Thank you for your feedback. Weight loss was observed in the studies of dipeptidyl peptidase-4 (DPP-4) inhibitors, as demonstrated by the mean change from baseline data, which are exaggerated when compared to a drug that shows weight gain. Appendix J provides input data used in the network meta-analyses of the absolute values for the mean changes from baseline in weight (kg). At initial therapy, studies of PP-4 inhibitors show absolute weight loss and gain at 12 and 24 months (Appendix J, tables 42 and 47). At first intensification, in the main, studies on DPP-4 inhibitors showed absolute weight loss at 12 and 24 months (Appendix J, tables 92 and 97). At second intensification, the 1 included study showed marginal absolute weight loss up to 12 months (Appendix J, table 128). Relative effects compared to a common comparator such as metformin-sulfonylurea at first intensification at 12 months that demonstrate absolute increases in weight from baseline (Appendix J, table 42; absolute mean changes from baseline ranged from -0.9kg to 1.94kg in 6 studies with an average of 0.975kg) would exaggerate the observed absolute

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							decreases in weight from baseline for DPP-4 inhibitors. Based on the reviewed evidence, +2.5kg with metformin-sulfonylurea over 1 year is an overestimate: changes of +1.35kg at 1 year (see appendix F.3.5.3.2, table 39) and +0.90kg at 2 years (see appendix F.3.11.2.1, table 77) were observed.
286	SH	UK Clinical Pharmacy Association	Full	253	General	*Table 87* **Recommendation 61 –** Asking patients to meet 1% reduction HbA1c **AND** a 3% reduction in weight restricts the benefits that this class can offer. ABCD have provided evidence that a 1% reduction HbA1c **OR** a 3% reduction in weight offers as much benefit. To set such arbitrary values undermines the clinical outcomes and evidence base. Studies that consider weight loss note that it is actual KG (eg every 10kg loss) of weight loss that lead to improved outcomes in blood glucose control, lipid profile and blood pressure control. Stopping a medication because the weight loss is for example 8% but the total weight loss is 12 kg would be inappropriate. Table 87 indicates that this decision was based entirely on cost and that no further evidence was considered. (Refs: http://www.diabetologists-abcd.org.uk/GLP1_Audits/ABCD_Hot_Topics_2012.pdf, KY Thong, P Sen Gupta, ML Cull, KA Adamson, DS Dove, SV Rowles, S Tarpey, C	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach

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						Duncan, J Chalmers, R Harper, P McDonald, U Brennan, C Walton, REJ Ryder on behalf of the ABCD nationwide exenatide and liraglutide audit contributors. NICE guidelines versus clinical practice – GLP-1 receptor agonists in type 2 diabetes Br J Diabetes Vasc Dis 2014; 14: 52-59) Is 1.8mg Liraglutide being allowed here from now on? This will overwrite the current NICE TA which states it is not cost effective, has this changed? If not I think it very important to add this into this section.	to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level. NICE clinical guidelines do not usually make reference to dosage of any drug. The GDG did not consider the evaluated evidence permitted differing recommendations for particular preparations or dosages of GLP-1 treatment options, alongside metformin-

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							sulfonylurea. The TA203 recommendation prohibiting the use of liraglutide at 1.8mg has been updated and replaced by this guideline.
259	SH	South Sefton Clinical Comissioning Group	Full	256	19	It is worth reviewing the diagnosis as patients with a fairly recent diagnosis of Type 2 Diabetes may have latent Autoimmune Diabetes of Adults whilst those with a long history or who have had over conditions affecting the pancreas such as recurrent episodes of pancreatitis may have no beta-cell function.	Thank you for your feedback. The guideline development group agreed that these patients would be identified in routine clinical follow-up and would not be treated differently.
104	SH	Central Manchester University Hospitals NHSFT	Full	258	15	Consider lowering BMI threshold for starting GLP-1 to 30 or not having BMI cut-offs. NICE recommends assessment for bariatric surgery for people with a BMI of 30–34.9 who have recent-onset type 2 diabetes – so why not start GLP agonists at this stage? GLP-1 agonists are suitable second line for some patients as supported by American Diabetes Association and European Association for the Study of Diabetes. Many clinicians do not follow the reassessment criteria as patients may lose less than 3% weight or less than 1% improvement in HbA1c but the agents are very useful to the individual, especially where preventing weight gain (e.g. if the patient is on insulin / SU) is important.	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal

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							(and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. The GDG recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed

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							the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
158	SH	Leeds North Clinical Commisioning Group	Full	258	15-26	Query re recommendation '*If triple therapy with metformin and 2 other oral drugs (see recommendation 59) is not effective, tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes'.* This is different to current DM pathway TAs for liraglutide and exenatide SR, where GLP-1 agonists are recommended in dual therapy e.g. ''*Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulphonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:* • *the person is intolerant of either*	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model,

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						*metformin **or** a sulphonylurea, or treatment with metformin or a sulphonylurea is contraindicated, **and*** • *the person is intolerant of thiazolidinediones **and** DPP-4 inhibitors, or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.* *Treatment with liraglutide 1.2 mg daily in a dual therapy regimen should only be continued if a beneficial metabolic response has been shown (defined as a reduction of at least 11 mmol/mol [1 percentage point] in HbA_{1c} at 6 months). The recommendation for exenatide SR is similar.* So the updated guidance and algorithm place them after triple oral therapy, rather than as a dual therapy option we thought this was confusing as their place in the algorithm is different to the recommendations in the TAs.	which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option. The GDG noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with

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							due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
161	SH	Lilly UK	Full	258	15	Same as previous comment: *We are concerned that the body mass index (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 clinical justification for restricting the use of GLP-1 RAs to patients above a certain BMI.*	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in

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							HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
16	SH	Lilly UK	Full	258	27	Same as previous comment:	Thank you for your feedback. This guideline

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3						*The continuation rules for the GLP-1 RAs which include targets for both glycated haemoglobin (HbA1c) and weight have been retained. We still believe that the 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.*	updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s

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							may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
105	SH	Central Manchester University Hospitals NHSFT	Full	258	General	In practice, long acting GLP-1 agonists (Bydureon) seem more effective than short acting with less side effects.	Thank you for your feedback. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the guideline development group was not convinced of the purported material differences between the various preparations.
103	SH	Central Manchester University Hospitals NHSFT	Full	259 General	1 -5	We feel that the lack of SGLT2 as a formal option is a weakness in new guidance and that these treatment options should be included fully rather than referenced to the technology appraisals.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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

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							area and should assure quick navigation between recommendations on type 2 diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information.
106	SH	Central Manchester University Hospitals NHSFT	Full	259	30	Current guideline suggests change of NPH to analogue insulin if the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes. We suggest nocturnal and other silent hypoglycaemia are equally valid reasons for considering analogues.	Thank you for your feedback. The guideline development group agreed that hypoglycaemic episodes including nocturnal and silent hypoglycaemia become important when they affect the individual, becoming symptomatic.
74	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	Full	262	General	*Research recommendation 11, 8.4.18:* This recommendation is in response to ABCD feedback in round 1. We welcome this, but would suggest that pharmaco-genetic determinants be included.	Thank you for your feedback. This area was not identified as a gap in the process and the guideline development group did not considered it a priority at this iteration of the guideline update.
134	SH	Janssen	Full Appendix J	General	General	Although NICE has acknowledged the limitations of using a CUA model such as the OM1, which has been superseded by newer models (e.g. CORE and ECHO) accounting for the most recent clinical practice habits; NICE does not appear to accept any challenge posed in the previous consultation process regarding the network meta analysis (NMA) methodology. Janssen would however like to raise the identified issues to NICE's attention for a second time as some	Thank you for your feedback. As explained in section 8.4.1.4 (full guideline), the guideline development group (GDG) 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

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						assumptions and approaches used in the development of the NMA informing this guideline do not appear wholly aligned with best practice principles as outlined by the ISPOR Task Force Good Practice Reports [Janssen et al (2011); Hoaglin et al (2011)] and the Decision support Unit [Dias et al (2014)]. There are many caveats in performing a valid NMA. By combining studies, a meta-analysis increases the sample size and thus the power to study effects of interest; however, in some cases the results can be misleading. Diabetes is a notoriously challenging area in which to conduct indirect comparisons and NMAs. While there is a great deal of information, the evidence is not evenly distributed across therapies and lines of treatment. Methods used in NMAs are evolving, particularly regarding the use of Bayesian statistics. The NICE analysis team has done a great deal of work to draw together a complex evidence base. Nevertheless, it appears there are specific issues regarding some of the assumptions and technical approaches used to inform this analysis that deserve further consideration to determine their appropriateness given the complexity of the disease area and richness and diversity of the evidence base.	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 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.

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						The Guideline Development Group (GDG) approach ignores all indirect evidence via placebo for the intensification networks; e.g. all oral anti-diabetic (OAD) + metformin (MET) versus placebo (PBO) + MET trials would not be included in the first intensification network, ignoring a substantial portion of the clinically meaningful evidence base. The inclusion of these trials may have allowed more precise estimates to be made, as a large majority of the evidence base is made up of trials, traditionally used for clinical decision making, that compare against PBO. And yet, it is also possible that the inclusion of additional trials increases clinical heterogeneity, which may introduce unhelpful statistical inconsistency into the models. The GDG appear to dismiss substantial heterogeneity between trials; which may elicit unexpected results and recommendations such like the recommendation of repaglinide early in therapy, owing to the inappropriate pooling of patient populations not accounting for variability such as: ➢ the potential for change in patient characteristics over time (i.e. older trials may be different); ➢ the difference in trial populations (e.g. different nationalities, obese versus non-obese);	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. Some studies included mixed populations of drug naïve and experienced individuals, and where separate results are reported, relevant data for drug naïve individuals were extracted. The sample sizes of the subgroups of individual studies are typically quite small. To increase the statistical power, a sensitivity analysis of all the available pooled data was undertaken. Heterogeneity between trials was evaluated using the GRADE assessment and considered by the GDG, with deliberations documented in the 'Linking evidence to recommendations' tables as appropriate.

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						➢ the different stages of the disease (i.e. treatment naïve and experienced patients); and ➢ the difference in trial design (e.g. inconsistent trial results due to limited data and high drop-out rates) Whilst the analysis does use random effects, there are not sufficient data to provide robust estimates and, as such, there is a marked risk of unmeasured and/or unaccounted heterogeneity. In summary, the recommendations seem do not appear entirely justified given diabetes expert understanding and appear wholly driven by the analysis. It must be understood that a CUA is only ever as good as the data that informs it. In this respect, if there is uncertainty around the assumptions and evidence used to conduct the NMA informing the CUA, this uncertainty will only amplify when incorporated into further probabilistic analyses. The principal reasons for the uncertainty in the NMA informing the clinical guideline (CG) update are the omission of relevant data (the CG scope does not include all anti-hyperglycaemic agents currently available and used in the UK) and the included data have been synthesised in a way that ignores current clinical practice (guideline development issue).	
193	SH	Newcastle University	Full Economics	153	Figure 23	The symbol coding chosen for the met-pio line is unfortunate – below k£40 where it is most	Thank you for your feedback.

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			report			important it does not appear to match the key – it only works as the line flattens out.	
53	SH	Primary Care Diabetes Society	NICE	General	General	Sulphonylurea and repaglinide therapies still have a strong influence in the draft guideline. These therapies cause significant concern regarding weight gain, hypoglycaemia risk and adverse cardiovascular outcomes. . Although these are useful therapies , their use in many at risk Type 2 diabetics causes concern and cautionary notes should be made when these are suggested. Repaglinide is a therapy that can be complicated in dose titration and ideally is three times daily. This can cause confusion and significant compliance issues. It also only has a licence to use with Metformin. The place of Repaglinide as an equal agent to other therapies at intensification should be reviewed. Emphasis should also be made for regular glycaemic review and the consideration of dose reduction when using Sulphonylurea or repaglinide therapies by taking into account the risks of diabetes duration, renal impairment, cardiac disease and the patient's age.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification. The guideline development group disagrees that sulfonylureas in particular are prominently placed in the recommendations and algorithm. It is unclear how sulfonylureas can be less prominent at intensification phases without complete removal. Other antihyperglycaemic medicines are associated with weight gain, hypoglycaemic risk and adverse cardiovascular outcomes. However, the treatment options have been re-ordered alphabetically.
54	SH	Primary Care Diabetes Society	NICE	General	General	The emphasis of the guidance continues to address a reactive approach to managing diabetes – waiting for failure before intensification.	Thank you for your feedback. The guideline development group (GDG) disagrees that the guideline promotes clinical inertia.

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						There is strong evidence surrounding clinical inertia for diabetes intensification. The guideline should emphasis a target lead , proactive approach to management. The Lipid guideline suggests 3 monthly blood tests and intensification of therapy if target not reached. This approach may not be suitable in a patient with diabetes, but a joint management plan with a suggested rate of intensification should be advised.	Within the guideline, regular review with reinforcement of diet, lifestyle and adherence to treatment is recommended, along with consideration to stop ineffective medicines. The GDG also recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). The GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals appropriate target and intensification HbA1c levels.
55	SH	Primary Care Diabetes Society	NICE	General	General	The Primary Care Diabetes Society have reviewed the new draft and feel that there has been a significant improvement. We congratulate the committee for its review and further consultation. However, the guideline must be suitable for use by specialists and clinicians with less experience in diabetes management. We remain concerned that the draft guideline has several errors as highlighted in the above comments. We are concerned that as it currently stands, following the guideline can still lead to errors in patient management. With the newer cardiovascular safety studies for DPP4-inhibitors and the SGLT-2 agents having no formal inclusion	Thank you for your feedback. The guideline development group has considered the issues raised by stakeholders at the second consultation, particularly with respect to the pharmacological management of blood glucose and have made further amendments to the algorithm and recommendations to facilitate evidence-based guidance that is user-friendly to a wide range of stakeholders including non-specialists. Long-term drug safety (including cardiovascular outcomes) was considered in a separate review question, with a search date cut off of June 2014.

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						within the guideline, it will already be considered as dated by clinicians with experience in diabetes care.	Any studies published after this date could not be included in this update. The recent TECOS study (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) does not meet the inclusion criteria as a proportion or all patients were taking pre-existing oral antidiabetic drugs/insulin (confounding) and comparisons are likely to be across treatment phases. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
108	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	General	General	The guidance is considered a much more practical than the previous guidance but with a number of areas in which improvements could be made particularly in the presentation of the pharmacological algorithm	Thank you for your feedback. The guideline development group has considered the issues raised by stakeholders at the second consultation, particularly with respect to the pharmacological management of blood glucose and have made further amendments to the algorithm and recommendations to facilitate evidence-

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							based guidance that is user-friendly to a wide range of stakeholders including non-specialists.
122	SH	Diabetes UK	NICE	General	General	We are concerned that there is no clear guidance on making people aware of the effect of sulphonylurea on weight gain and hypoglycaemia for them to make an informed choice, given that sulphonylureas have now been given real prominence throughout the treatment pathway. We also suggest that, this prominence which has now been given to sulphonylureas should be downgraded.	Thank you for your feedback. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. The guideline development group disagrees that sulfonylureas in particular are prominently placed in the recommendations and algorithm. It is unclear how sulfonylureas can be less prominent at intensification phases without complete removal. However, the treatment options have been re-ordered alphabetically.
123	SH	Diabetes UK	NICE	General	General	There are real concerns about the risk of bladder cancer with pioglitazone and we are concerned that, if this is not explained properly to people with diabetes, it may lead to non-compliance.	Thank you for your feedback. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: • heart failure or history of heart failure , • hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015]

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							A footnote on the safety alerts for pioglitazone was added, and a note to exercise particular caution if the person is at high risk of the adverse effects of this drug. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action.
124	SH	Diabetes UK	NICE	General	General	SGLT-2 should be added in the main guidelines as an option across the treatment pathway rather than a cross-reference to the technology appraisals. Clinicians and patients find it unhelpful to have partially updated guidelines with links to other external documents. It will be more practical to have the guidance on SGLT-2 fully incorporated, and readily accessible, otherwise we are concerned that this aspect of the guidelines risks being overlooked. This could lead to people with diabetes being denied access to this new group of drugs which can help them to achieve their targets and reduce their risk of devastating complications.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
130	SH	Diabetes Reference Group Conwy and Denbighshire	NICE	General	General	*1.7.13:* The detailed guidance here regarding erectile dysfunction in men is welcomed. However, we can't find any reference to ***female*** sexual dysfunction in the document. It is widely acknowledged that diabetes can cause loss of libido and other physical issues for women	Thank you for your feedback. It was not within the scope of the guideline at this update to consider female sexual dysfunction. However, this important issue has been recognised by the guideline development group and covered in the equality impact assessment of the

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						with diabetes, so this should be dealt with in the guidance. This of course could have a knock-on effect on the wellbeing of the patient's partner.	guideline. A research recommendation "What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction related to type 2 diabetes in women?" has been included in the guideline. This topic will be flagged to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.
131	SH	Janssen	NICE	General	General	Janssen welcomes the second opportunity to respond to the draft NICE clinical guideline (CG) update for the management of patient with type 2 diabetes (T2d). First and foremost, Janssen recognises that there have been considerable improvements made to the guideline following the first consultation, specifically with reference to the pharmacotherapy treatment algorithm. The general consensus of the draft guideline is that of individualised care; however Janssen believes that the recommendations and treatment algorithm relating to pharmacotherapy still falls short of the high standard set by the well-established and respected position statement issued by EASD/ADA [Inzucchi, et al 2015], as well as the recently published American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology Clinical Practice Guidelines [Handelsman, et al 2015], which focus on developing a comprehensive Care Plan for patients with T2d.	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. The pharmacological blood glucose lowering therapies review included drug classes and specific drugs as listed in the guideline scope, for example, acarbose, sulfonylureas. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes, and considered short and long-term outcomes such as change in HbA1c, rates of hypoglycaemia, change in body weight and cardiovascular outcomes. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The guideline development group (GDG) was clear that heterogeneous prescribing practice – especially at later stages of the

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						Janssen would like to understand the apparent omission of 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. It appears there are important changes still needed as the proposed treatment algorithm is misaligned with other NICE guidance and could lead to clinician confusion and sub-optimal care.	treatment pathway – is commonly driven by prescriber habit, rather than true differences in clinical circumstances. For this reason, the GDG wanted to provide more specific guidance for healthcare professionals to support improved prescribing practices. Where appropriate, the GDG considered circumstances in which recommendations would benefit from tailoring in light of a range of baseline HbA1c levels and renal function, as detailed in the 'Linking evidence to recommendations' tables. The NICE developed type 2 diabetes guideline was able to take into account the costs of treatments through formal health economic modelling (including the need for self-monitoring of blood glucose levels), which sets this guideline apart from other internationally recognised guidelines.
165	SH	Merck Sharp & Dohme UK	NICE	General	General	**General comments** MSD would like to thank the guideline development group (GDG) for the opportunity to comment on this second draft of the Type 2 Diabetes Guideline (CG87). The overwhelming response from stakeholders, inclusive of MSD, illustrates the importance of this guideline and the complexity of managing patients with type 2 diabetes mellitus (T2DM).	Thank you for your feedback.

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						MSD agree that this revised version of the guideline reflects an improved patient-centric approach and welcomes several key changes, namely: • The equal positioning of DPP-4 inhibitors, pioglitazone, repaglinide, and sulfonylureas at initial drug therapy when metformin is contraindicated or not tolerated. • The equal positioning of DPP-4 inhibitors, pioglitazone and sulfonylureas at first intensification of drug treatment when initial drug therapy with metformin has not continued to control HbA1c. • The addition of a simplified treatment algorithm (algorithm figure, page 23). • The inclusion of MHRA safety warnings within both the guideline text and algorithm. • The inclusion of text to assist HCPs identify the benefits and risk of drug treatment (section 1.6.17). • The inclusion of appropriate cross referencing to relevant technology appraisals, which will preserve the validity of this guideline during their maintenance/ update.	
177	SH	National Diabetes	NICE	General	General	Why are Hba1c measurements in % still being included the switch to mmol/mol took place in	Thank you for your feedback. To ensure NICE guidance is as clear as possible to

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		Nurse Consultant Group				2011 and this is promoting the use of outdated terminology.	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.
178	SH	National Diabetes Nurse Consultant Group	NICE	General	General	*Algorythim; Between 22-23* First intensification Metformin tolerated – suggest if HbA1c increases bu more than 5mmols/mol- 58 an increase of 10mmols/mol before seconf treatment commenced	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.
171	SH	National Diabetes Nurse Consultant Group	NICE	3	10	Prevalence is 3.9 million now	Thank you for your feedback. Diabetes UK does not provide the source for the 3.9 million estimate, which is assumed to be for people diagnosed and undiagnosed with diabetes. Within the document (page 3, prevalence section), it quotes the 2012/2013 Quality and Outcomes Framework prevalence figures which are used in the guideline.

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277	SH	Training, Research and Education for Nurses in Diabetes	NICE	3	10	Prevalence is 3.9 million now	Thank you for your feedback. Diabetes UK does not provide the source for the 3.9 million estimate, which is assumed to be for people diagnosed and undiagnosed with diabetes. Within the document (page 3, prevalence section), it quotes the 2012/2013 Quality and Outcomes Framework prevalence figures which are used in the guideline.
172	SH	National Diabetes Nurse Consultant Group	NICE	3	General	*Last line* Add "does not cover CKD" please	Thank you for your feedback. Recommendation 1.7.12 (NICE short version) cross-refers to the Chronic kidney disease NICE guideline 182. 1.7.12 For guidance on managing kidney disease in adults with type 2 diabetes, see the NICE guideline on chronic kidney disease. [new 2015]
278	SH	Training, Research and Education for Nurses in Diabetes	NICE	3	General	Last line Add "does not cover CKD" please	Thank you for your feedback. Recommendation 1.7.12 (NICE short version) cross-refers to the Chronic kidney disease NICE guideline 182. 1.7.12 For guidance on managing kidney disease in adults with type 2 diabetes, see the NICE guideline on chronic kidney disease. [new 2015]
26	SH	Successful Diabetes	NICE	8	9 10	Welcome and encourage the idea to create a standing update committee on diabetes	Thank you for your feedback.
60	SH	British Medical Association	NICE	10	General	1.6.5 We welcome the setting of targets in partnership with patients.	Thank you for your feedback.

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109	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	10	3	As well as indicating a target BP> 140/80 should there be an indication of a level below which BP should not be lowered to avoid overtreatment?	Thank you for your feedback. It was not within the scope of the guideline at this update to consider hypertension. This topic will be flagged to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.
110	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	10 20	26 10	'while driving or operating machinery' seems a rather limited and over specific definition and might be better rephrased as 'while driving or participating in any activity which might put the individual or others at significant risk in the event of the effects of hypoglycaemia. There are many activities occupational or otherwise which might fall into such a category.	Thank you for your feedback. The guideline development group considered the phrase adequate in providing guidance on when self-monitoring of blood glucose should be offered.
65	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	10	37	ABCD would welcome the establishment of a standing update committee for diabetes to enable responsive updating of sections of the guideline. This will be particularly important to maintain credibility if the T.A.s for newer agents are not incorporated into this update. There are several cardiovascular outcome studies for newer agents due to report in the near future that may necessitate a rapid response.	Thank you for your feedback.
166	SH	Merck Sharp & Dohme UK	NICE	11 23-25	General	**Consistency of wording throughout the short guideline document** MSD commend the equal positioning of DPP-4 inhibitors, pioglitazone, repaglinide, and sulfonylurea at: • "Initial drug therapy in adults with type 2	Thank you for your feedback. The order of the treatment options was originally based on the evaluated clinical and cost-effectiveness evidence. However, the treatment options have now been re-ordered alphabetically.

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						diabetes, if metformin is contraindicated or not tolerated…" MSD commend the equal positioning of DPP-4 inhibitors, pioglitazone, and sulfonylurea at: • "First intensification if initial drug treatment with metformin has not continued to control HbA1c …" The equal positioning of the aforementioned technologies fully reflects the complexities associated with the care of patients with T2DM and promotes an individualised patient approach. This flexibility provides HCPs with a breadth of prescribing options when choosing the most clinically appropriate treatment for patients and will enable improved care above and beyond a "one size, fits all approach". However, MSD have noticed several inconsistencies within the short guideline document. It is possible that these inconsistencies between; the text and treatment algorithm; listing of possible treatment options; and listing of treatment combinations at stages of intensification could confuse HCPs and advocate a hierarchical prescribing pathway, which is not the recommendation of the GDG. MSD recommend that these be corrected to ensure consistency and enhanced readability by	The recommendations and algorithm have been checked to ensure the consistent use of terms such as 'or'.

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						individuals in the NHS. MSD ask • When considering drug treatment options, these should be listed alphabetically. For example treatment options are listed alphabetically on page 11, Drug treatment; page 23, box 1 (metformin contraindicated or not tolerated) and page 24 section 1.6.23. However, it appears that treatment options are not listed alphabetically within the treatment algorithm on page 23, box 2 (first intensification, patients who can take metformin); box 3, (second intensification); box 2, first intensification (metformin contraindicated or not tolerated); page 24, section 1.6.24; and page 25, section 1.6.25. MSD ask • That the use of "**or**" when advising HCP to consider a treatment option is consistently applied (i.e. when multiple treatment choices are available and positioned equally), for example "**Or**" is already consistently used on page 24 section 1.6.23, section 1.6.24; and page 25 section 1.6.25, section 1.6.26. However, the treatment algorithm on page	

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						23 does not use "**or**" within the first and second intensification boxes for patients who can initiate treatment with metformin and is therefore inconsistent with section 1.6.23 and 1.6.24. Similarly within the initial and first intensification boxes of the metformin contraindicated algorithm, the use of "**or**" is not consistent with the full text in section 1.6.25.	
186	SH	Newcastle University	NICE	11 24	General	*1.6.23 & 1.6.24* Why DPP-4i's are recommended as a free choice for monotherapy if metformin is contraindicated or for first intensification – how can this be cost-effective? Your figures show for the class incremental costs of £1200 over the previously recommended (2009) sulfonylureas (using first intensification data) and no consistent QALY gain across the class (Full economics report 4.5.3/4.5.4). I would be the last to suggest the ICER is infinite (the error intervals are very large, and you miss some issues such as the savings from better tolerability), but more justification is needed before raising total diabetes costs by 6% from this stage of disease. In fact section 4.8 of the Full economics report fails to justify this decision (first intensification), as does the Full guideline (see next point). We have to be concerned to about affordability as well as very	Thank you for your feedback. Section 8.4.7 of the full guideline outlines the guideline development group (GDG)'s rationale for recommending alternatives to metformin for initial therapy. The GDG noted that Medicines and Healthcare products Regulatory Agency (MHRA) guidelines and patient suitability (including treatment-related weight gain over and above that considered generically in the health economic modelling) should be considered when individualising care. The evaluated evidence indicated that if the choice is between sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors, the pairwise probabilistic comparisons of treatment options (appendix F figure 20) suggest there is little difference between sulfonylureas and sitagliptin.

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						poor cost-effectiveness – this is tens of millions of pounds per year, and must be better justified or limited to sulfonylurea intolerability situations. Meanwhile we note sulfonylureas have positive CV and death outcome data from the extension of UKPDS, while DPP4is have never been tested in a typical (as opposed to selected, and short-term) type 2 diabetes population for true outcomes.	Long-term drug safety (including cardiovascular outcomes and mortality) 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. The recent TECOS study (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) does not meet the inclusion criteria as a proportion or all patients were taking pre-existing oral antidiabetic drugs/insulin (confounding) and comparisons are likely to be across treatment phases.
61	SH	British Medical Association	NICE	12	General	*1.1.1* We welcome the individualised care approach taking into account the likelihood of the patient to benefit from interventions	Thank you for your feedback.
66	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	12	General	*1.3.4.1 Targets:* – What is justification for not intensifying treatment on single drug treatment until HbA1c rises to 58 mmol/mol? This is particularly important for younger people, who are likely to gain more benefit from glycaemia reduction with less disutility than older people, and exploits the legacy effect of early good glycaemic control on long term outcomes.	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would

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							then be able to discuss with individuals, appropriate target and intensification HbA1c levels. In addition, within the guideline, regular review with reinforcement of diet, lifestyle and adherence to treatment is recommended, along with consideration to stop ineffective medicines. Further details are provided in the 'Linking evidence to recommendations' table in section 8.1.3 in the full guideline.
155	SH	Leeds North Clinical Commisioning Group	NICE	12	General	1.1.1 We agree with the individualised approach to diabetes care which is tailored to the needs and circumstances of the patient. We like the fact that you have recommended that this is reassessed at each review with consideration to de-prescribing medication which is ineffective. This will hopefully reduce polypharmacy and side effects in individual patients at the same time as reducing the costs from wasted medicines.	Thank you for your feedback.
67	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	13	19	*1.3.5:* The benefits, if any, of using repaglinide would seem to be outweighed by the disadvantages. Does the evidence really justify its special mention vs SUs? The prandial dosing schedule is likely to result in reduced adherence. The complex dose titration schedule, supported by capillary blood glucose monitoring and visits to clinic will limit its uptake.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-

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							effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
72	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	14 20	24	*Algorithm, rec 55:* Metformin – Safety note. For patients who are admitted to hospital with Acute Kidney Injury (AKI), metformin will need to be discontinued temporarily. On recovery from AKI and with eGFR > 30 mL/min/1.73m^2, it can be restarted safely.	Thank you for your feedback. This is part of normal clinical practice. There are other reasons when one might suspend treatment and these have not been outlined.
111	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	14	26	'low fat dairy products' there is increasing concern about the amount of sugars in low fat yoghurts and uncertainty about the benfits of restricting dietary fat so does recommending low fat dairy products still stand upto rigorous scientific scrutiny?	Thank you for your feedback. It was not within the scope of the guideline at this update to consider diet. 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. This topic will be flagged to the NICE surveillance team for consideration during the next iteration of the type 2 diabetes guideline.
68	SH	Association of British Clinical Diabetologists (endorsed by Royal College of	NICE	14	General	*Algorithm:* Differential targets – for initial pharmacological treatments vs first and second intensifications. See P12 1.3.4.1	Thank you for your feedback. Different HbA1c levels have been set for initiating pharmacological treatments in individuals whose blood glucose levels are inadequately controlled by diet and exercise alone. As the condition progresses, drug treatment intensification

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		Physicians)					HbA1c levels are higher as blood glucose levels continue to be inadequately controlled by diet/exercise and a single drug.
69	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	14	General	*Algorithm:* Insulin-based treatment In the 4T Study – use of pre-mixed insulins was the least good option vs basal only or prandial insulin. In addition, in younger individuals, the impact on loss of flexibility and a higher risk of hypoglycaemia with pre-mixed insulin is a major barrier to intensification of insulin treatment to targets. This is not acknowledged in the guideline. RR Holman, AJ Farmer, MJ Davies et al Three year efficacy of complex insulin regimens in Type 2 diabetes. N Engl J Med 2009; **361**:1736-47.	Thank you for your feedback. The 4T study did not meet the review's inclusion criteria because a proportion or all patients taking pre-existing oral antidiabetic drugs (contamination) or other oral antidiabetic drug/insulin (with no subgroup analyses) [see Appendix L, row 337].
70	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	14	General	*Algorithm:* Combination preparations – Metformin plus another licensed agent - are increasingly being marketed. ABCD believes that there may be a place for use of these combination drugs given the polypharmacy associated with diabetes management. The GDG should comment specifically on this, if only to acknowledge the existence of such combinations and some comments as to the situations where use of combinations is justified.	Thank you for your feedback. Combination preparations were not reviewed in the guideline.
71	SH	Association	NICE	14	General	*Algorithm:*	Thank you for your feedback. Long-term

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		of British Clinical Diabetologists (endorsed by Royal College of Physicians)				Pioglitazone: This agent is acknowledged and is given equal weighting by the guidance and we are supportive of this. However, the new publication of studies in relation to this drug suggests no increased risk of bladder cancer and this should be reflected in the guideline. Lewis et.al. *JAMA.* 2015;314(3):265-277. doi:10.1001/jama.2015.7996	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. The link to the Medicines and Healthcare products Regulatory Agency (MHRA) in the recommendations should help users keep updated with safety issues.
73	SH	Association of British Clinical Diabetologists (endorsed by Royal College of Physicians)	NICE	14	General	*Algorithm:* Gliflozins: ABCD believes that not embedding this class of drugs in the flow chart is a significant omission, and is a departure from the original scope of the update. The brief reference in footnote 3 exhorting clinicians to read another document and place the class separately from the body of the main algorithm is illogical and will discredit the update as a resource for busy clinicians.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
132	SH	Janssen	NICE	14	General	Treatment algorithm; In line with the ADA/EASD and the AACE guidelines, it is important to ensure that clinicians have the flexibility to prescribe medicines for type 2 diabetes according to the individual needs of their patients. While the draft guideline recognises	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. The pharmacological blood glucose lowering therapies review included drug classes and specific drugs as listed in

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						this, it also restricts the treatment options that are available. It is expected that most general practitioners will refer to the pharmacotherapy treatment algorithm as a main point of reference, assuming that the treatment algorithm summarises the general position of the clinical guideline as well as the pharmacotherapy treatment recommendations. Therefore, it is important that the treatment algorithm reflects the entirety of the updated clinical guideline and not only the cost-utility analysis conclusions. It is probable that, given the way in which the NICE guidelines are applied locally, therapy options may be limited and patient may receive treatments that are inappropriate given the patient's predispositions and comorbidities. This could result in a protracted wait for the most appropriate medicine for the individual. Janssen welcomes the incorporation of SGLT2 inhibitors into the algorithm, however would like to understand the rationale for limiting the reference to the latest technology appraisals (TAs) to the footnotes, where many unaffiliated matters are discussed, rather than incorporating them into the treatment algorithm and pharmacotherapy recommendations directly as per the TAs recommendations. Janssen acknowledges that SGLT2 inhibitors were not included in the evidence review as part of the development of this guideline. In order to avoid confusion among	the guideline scope, for example, acarbose, sulfonylureas. Recommendations and the algorithm are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes and considered short and long-term outcomes such as change in HbA1c, rates of hypoglycaemia, change in body weight and cardiovascular outcomes. Recommendations are not only based on all available licensed options/combinations. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The guideline development group (GDG) was clear that heterogeneous prescribing practice – especially at later stages of the treatment pathway – is commonly driven by prescriber habit, rather than true differences in clinical circumstances. For this reason, the GDG wanted to provide more specific guidance for healthcare professionals to support improved prescribing practices. 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.

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						healthcare professionals, however, we advocate that that the findings of the TAs for the SGLT-2 inhibitors are made appropriately clear throughout the guideline, particularly within the pharmacotherapy recommendations and treatment algorithm. The CG should act as a single point of reference for the generalist reader of the clinical guideline. Reference boxes and footnotes 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 unexploited opportunities to provide most appropriate treatment for an individual and may result in a negative impact on health outcomes. In parallel, practitioners within primary care may find it difficult to identify the most appropriate treatment 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 use of any medicine in patients with Type 2 diabetes should 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. Thus, Janssen would like to restate concern that the encouragement to use the cheapest agent within	Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. Recommendation 1.6.17 (NICE short version) provides a list of factors to consider when selecting drug treatments, not only acquisition costs. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical

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						each class can have negative consequences for patients, in that they are potentially denied the most effective treatment in class. 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. In summary, delaying access for patients to newer anti-hyperglycaemic agents in the treatment paradigm could adversely affect patients' long-term outcomes. It was reported that early successful control of both blood glucose and concomitant comorbidities; e.g. weight change and increased blood pressure, can substantially improve long-term outcomes in patients with T2d [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 patient needs. Janssen believe it is a patient's prerogative to receive the best available treatment that tailored	circumstances, for example, comorbidities, risks from polypharmacy • the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [new 2015] The suggestion of a patient decision aid has been passed on to NICE implementation team.

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						to their needs in the first instance.	
133	SH	Janssen	NICE	14	General	*Treatment algorithm;* Janssen appreciates that glucose control remains a key clinical outcome in the management of patients with type 2 diabetes. However, Janssen believe that within the revised pharmacotherapy treatment algorithm still insufficient focus has been placed on management of secondary outcomes. Janssen would like to re-iterate that 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 acquisition cost. The cost-utility analysis (CUA) largely used to inform the pharmacotherapy treatment algorithm 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 remains unclear and would like to understand why outcomes considered previously as indicators of success in the treatment of diabetes have not been considered within the cost-effectiveness analysis. Moreover, the Pharmaceutical Price Regulation Scheme (PPRS) agreement presents the NHS with the opportunity to increase the availability and use of the branded medicines. The costs of	Thank you for your feedback. Individualised care does not preclude guidance on clinically and cost-effective treatment options. The pharmacological blood glucose lowering therapies review included drug classes and specific drugs as listed in the guideline scope, for example, acarbose, sulfonylureas. Recommendations are based on the available clinical evidence and health economic modelling for the specified drugs and/or classes and considered short and long-term outcomes such as change in HbA1c, rates of hypoglycaemia, change in body weight and cardiovascular outcomes. Recommendations are not only based on all available licensed options/combinations. The purpose of the evidence review and recommendations was to provide specific guidance on optimal treatment options and/or combinations. The guideline development group (GDG) was clear that heterogeneous prescribing practice – especially at later stages of the treatment pathway – is commonly driven by prescriber habit, rather than true differences in clinical circumstances. For this reason, the GDG wanted to provide more specific guidance for healthcare

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						prescribing branded medicines over agreed growth levels are underwritten by the pharmaceutical industry, which allows clinicians to have greater flexibility to prescribe newer, more innovative medicines to best suit patients medical needs, Thus, acquisition cost should not feature prominently as a decision influence. The latest draft of the guideline considers a number of factors for medical professionals to consider when selecting the right treatment for their patient. However, within the revised pharmacotherapy treatment algorithm there is still no reflection of this clinical decision making process. There is little consideration of a patient's risk of hypoglycaemia, baseline HbA1c, and choice. Any need for blood glucose monitoring or measurement of renal function is also unaccounted for within the algorithm in terms of disease management and cost consequence. Janssen welcomes the recognition within the CG that improved weight and hypoglycaemia rates can improve medical outcomes as well patents' quality of life, self-esteem and treatment satisfaction. In addition, considering that 90% of people with T2d are overweight, Janssen suggests that weight should be added to the list of considered factors when choosing the right therapy for patients. Different classes of T2d medicines can cause weight changes and so this	professionals to support improved prescribing practices. Where appropriate, the GDG considered circumstances in which recommendations would benefit from tailoring in light of a range of baseline HbA1c levels and renal function, as detailed in the 'Linking evidence to recommendations' tables. 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. Recommendation 1.6.17 (NICE short version) provides a list of factors to consider when selecting drug treatments, not only acquisition costs. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical

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						is an important element for healthcare professionals to consider. In addition, the CG fails to encourage the consideration of using oral anti-hyperglycaemic agents in combination with insulin. Combining different classes of treatment is important in type 2 diabetes as their different mechanism of actions each target different physiological aspects of the disease encouraging a cumulative approach to disease management. Combinations of oral treatments, for example with SGLT2 inhibitors, can help patients reach their individual treatment targets while reducing the amount of insulin required. Prescribing an SGLT2 inhibitor with insulin can improve glycaemic control, reduce body weight and reduce the amount of insulin needed, without considerably increasing the risk of hypoglycaemia. This is an important treatment combination option, particularly for patients with high BMI. Janssen requests that NICE ensures the information relating to treatment combinations with insulin is complete; in line with the CG objective of supporting an individualised approach in manage of patients with in T2d. Janssen, therefore, advocates that NICE ensure the final guideline fully supports an individualised treatment approach in type 2 diabetes, and that the treatment algorithm is closely scrutinised and	circumstances, for example, comorbidities, risks from polypharmacy • the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [new 2015] The health economic model considered those outcomes prioritised as critical and important by the GDG, that considered a range of adverse effects including weight and hypoglycaemia. The GDG chose to prioritise those outcomes they considered to be critical to this review question which was specifically focussed on managing HbA1c levels rather than other risk factors. 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. The GDG did not consider it helpful to evaluate outcomes (such as cholesterol or systolic blood pressure) where data are fragmented and would only be available for a limited number of treatment options in the decision spaces.

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						tested to ensure it provides clear, consistent direction consistent with other NICE STA Guidance and does not cause confusion amongst healthcare professionals fully aligned with the requirements of medicines optimisation.	In accordance with the NICE guidelines manual, medicines are costed in health economic models based on the Drug Tariff. Newer and more innovative medicines that are not included in guidelines can be evaluated in the NICE technology appraisal process. 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 relevant technology appraisals. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. As stated, the recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations (e.g. insulin and oral antihyperglycaemic

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							medicines) have been made. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification.
112	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	17	4	A case can be made for excepting the frail elderly from first line use of an ACE inhibitor because of the possibility of AKI during intercurrent illness and the difficulty in educating this group about 'sick day rules' which should include advice to temporarily stop ACE inhibitors during intercurrent illness to minimise risk of AKI. There appears to be no mention anywhere of the importance of avoiding dual blockade of the renin–angiotensin system which has been shown to be of no additional benefit and with some harm ref *Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials BMJ 2013;346:f360*	Thank you for your feedback. It was not within the scope of the guideline at this update to consider hypertension and 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.
126	SH	Diabetes Reference Group Conwy and	NICE	18	General	In terms of involving the patient in decisions about care, we think that it is important that GPs give clear guidance on how / when medications are to be taken and that pharmacies should label the	Thank you for your feedback. Frequency and timing of medications are given in the summary of product characteristics and should be discussed with the patient by

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		Denbighshire				medications accordingly. e.g. "Take one each day" when? Morning? Evening?	their healthcare professional.
266	SH	Training, Research and Education for Nurses in Diabetes	NICE	19	General	1.6.18 Advising that if HbA1c reaches 58mmol/mol should suggest a review of therapy is acceptable . The patient and clinician should then agree a target that is appropriate for the individual. Advising a level of 53mmol/mol could lead to further confusion.	Thank you for our feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.
29	SH	Aneurin Bevan University Health Board	NICE	19	General	1.6.18 Advising that if HbA1c reaches 58mmol/mol should suggest a review of therapy is advisable. The patient and clinician can agree a target that is appropriate for the individual. By adding Advising a level of 53mmol/mol is not necessary in an individualised care plan.	Thank you for our feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification

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							HbA1c levels.
42	SH	Primary Care Diabetes Society	NICE	19	General	1.6.18 Confusion may arise due to the lack of clarity with HbA1c target. It is advised that at an HbA1c of 58mmol/mol therapy should be reviewed regarding further intensification. The guidelines suggest, the patient and clinician should then agree a target that is appropriate for the individual. Advising a level of 53mmol/mol could lead to further confusion. It is felt that a target of less than 58mmol/mol is clearer rather than a new suggested target of 53mmol/mol.	Thank you for our feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.
117	SH	Diabetes UK	NICE	19	General	*Section 1.6.8* **HbA1c target** This recommendation suggests waiting until HbA1c levels rise beyond 58mmol/mol (7.5%) before intensifying treatment. 58mmol/mol (7.5%) is too high especially for newly diagnosed and evidence recommends targeting at anything above 53mmol/mol (7%). We are extremely concerned that intensification is being left too long especially in younger people with Type 2 diabetes who would benefit from achieving, and maintaining, a lower HbA1c target. Keeping this recommendation in its current form risks giving people the false sense of security that maintain	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.

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						HbA1c below 58mmol/mol is ideal when clear evidence suggest that for younger, fitter, people we should be aiming for lower HbA1c targets. We suggest that intensification should be considered when HbA1c rises above 53mmol/mol (7%) for more than 6months.	
173	SH	National Diabetes Nurse Consultant Group	NICE	19	General	*1.6.8* This reads that a second treatment should not be started until reaches 58mmool/mol- should read Hba1c increases by 5mmols/mol	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels.
267	SH	Training, Research and Education for Nurses in Diabetes	NICE	20	General	1.6.10 Investigation is needed to ensure that patient still has a degree of hypoglycaemic awareness and not just rely on patient's reporting of symptoms. More intensive blood glucose monitoring or continuous glucose monitoring (if available) would be appropriate to ensure safety.	Thank you for your feedback. The evidence review on self-monitoring of blood glucose (SMBG) indicated that compared to no SMBG, a small clinically non-meaningful change in HbA1c levels was observed. None of 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

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							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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
268	SH	Training, Research and Education for Nurses in Diabetes	NICE	20	General	1.6.13 Some patients who are not on insulin, nor at risk of hypoglycaemia can significantly benefit from blood glucose monitoring. If the patient is motivated and can demonstrate that blood glucose monitoring does improve diabetes control , then these patients should be encouraged to continue . The diabetes NSF has suggested that we should 'empower' our patients to achieve ideal control.	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
27	SH	Successful Diabetes	NICE	20 -21	General	1.6. 12 - 1.6.16 Anyone on repaglinide or a SU will be at risk of hypoglycaemia, particularly if they are striving for	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no

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						the blood glucose targets recommended and especially if they are achieving them or lower. These people must be offered the means to, and encouraged to perform self blood glucose monitoring, in relation to driving, operating machinery or indeed in any work or everyday physical activity (which they are encouraged to undertake more of for general health in repeated national guidance). It seems unacceptable to only offer SBGM when someone may already be experiencing hypoglycaemia, to confirm it, when it could be used to avoid it. The 1.6.16 guidelines on checking blood glucose monitoring technique and use made of results are fair and will help to ensure resources are used cost-effectively. I entirely support this approach. However, this guidance could equally apply for people who were using SMBG to monitor their lifestyle changes without being on insulin stimulating medication and might even help to avoid this step change in treatment. With the evidence about good control of blood glucose being vitally important from diagnosis, to avoid long term consequences and especially for young people with type 2 diabetes, the context of	SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.

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						this current guidance simply does not put the 'tools to do the job' in the hands of those with diabetes. These comments are very relevant to the pharmacological management of Type 2 diabetes because of the possibility of avoiding or minimising step changes in treatment and detecting and treating hypoglycaemia promptly and/or avoiding hypoglycaemia risk, when on certain medications, and ensuring continuing safety of the individual and others.	
30	SH	Aneurin Bevan University Health Board	NICE	20	General	1.6.10 Questioning is needed to ensure that patient has hypoglycaemic awareness and not accept patient's reporting of symptoms as unawareness of hypoglycaemia can be revealed to the patient especially if intensive blood glucose monitoring or continual glucose monitoring (if available) is undertaken and would be appropriate to ensure safety.	Thank you for your feedback. The evidence review on self-monitoring of blood glucose (SMBG) indicated that compared to no SMBG, a small clinically non-meaningful change in HbA1c levels was observed. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be

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							considered.
43	SH	Primary Care Diabetes Society	NICE	20	General	1.6.10 Investigation is needed to ensure that patient still has a degree of hypoglycaemic awareness and not just rely on patient's reporting of symptoms. High risk patients should be assessed for hypoglycaemic unawareness. More intensive blood glucose monitoring or continual glucose monitoring (if available) would be appropriate to ensure safety.	Thank you for your feedback. The evidence review on self-monitoring of blood glucose (SMBG) indicated that compared to no SMBG, a small clinically non-meaningful change in HbA1c levels was observed. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
31	SH	Aneurin Bevan University Health Board	NICE	20	General	1.6.13 Some patients who are not on insulin or at risk of hypoglycaemia can significantly benefit from blood glucose monitoring, especially when newly diagnosed. If the patient is motivated and demonstrates that blood glucose monitoring is helping them to improve or understand diabetes control then these patients should be encouraged to continue. Individual care plan!	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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

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							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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
44	SH	Primary Care Diabetes Society	NICE	20	General	1.6.13 Some patients who are not on insulin nor at risk of hypoglycaemia can significantly benefit from blood glucose monitoring. If the patient is motivated and can demonstrate that blood glucose monitoring does improve diabetes control, then these patients should be encouraged to continue. This can be of particular value at the initial diagnosis and education of the patient as well at each level of intensification. Often by advising patients to monitor blood glucose prior to adding newer therapies, they may be able to make significant lifestyle changes that can delay the need for additional therapies. The diabetes NSF has suggested that we should 'empower' our patients to achieve ideal control.	Thank you for your feedback. The evidence review indicated that self-monitoring of blood glucose (SMBG) compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
62	SH	British Medical Association	NICE	20	General	1.6.9 We welcome recognition of the appropriateness of reducing targets in certain patients.	Thank you for your feedback.
12	SH	Diabetes	NICE	20	General	*1.6.13:*	Thank you for your feedback. The evidence

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7		Reference Group Conwy and Denbighshire				We think that Self monitoring should be offered to Type 2 patients where the GP feels that the patient is likely to benefit from quick feedback and where the patient is able to assimilate and act on the results, rather than waiting for the HBA1c quarterly. Also in cases of new diagnosis and where the patient is likely to go ***hyper*** with the associated risk of ketoacidosis, this should be available.	review indicated that self-monitoring of blood glucose (SMBG) compared to no SMBG resulted in a small clinically non-meaningful change in HbA1c levels. None of 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. Therefore, the guideline development group made a strong "Do not routinely offer" recommendation for SMBG and highlighted specific instances when SMBG should be considered.
174	SH	National Diabetes Nurse Consultant Group	NICE	20	General	*1.6.9* It would be helpful if specific targets for the frail, and those with additional co- morbidities could be stated – reference to IDF targets for the Frail elderly would be helpful here	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). Evidence specifically in subgroups of the elderly i.e. frail or those with comorbidities was not identified. The GDG considered recommendation 1.6.9 which provides guidance on circumstances when target

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							HbA1c levels should be relaxed to be adequate in facilitating discussion with individuals to set appropriate target and intensification HbA1c levels.
279	SH	Training, Research and Education for Nurses in Diabetes	NICE	20	1	It would be helpful if specific targets for the frail, and those with additional co- morbidities could be stated	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations promoting individualised care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). Evidence specifically in subgroups of the elderly i.e. frail or those with comorbidities was not identified. The GDG considered recommendation 1.6.9 which provides guidance on circumstances when target HbA1c levels should be relaxed to be adequate in facilitating discussion with individuals to set appropriate target and intensification HbA1c levels.
169	SH	Merck Sharp & Dohme UK	NICE	21	General	*NICE page 21 section 1.6.12* *Full page 185 section 8.4.4.43* **<u>Self-monitoring of blood glucose</u>** **<u>The use of glinides and Sulfonylureas when driving</u>** MSD ask the GDG to provide additional	Thank you for your feedback. The guideline development group agreed that to future-proof the guideline, it would be useful to link to the DVLA as their position may change over time. Recommendation 1.6.12 (NICE short version) provides link to the DVLA guidance. 1.6.12 Take the Driver and Vehicle

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						clarification in section 1.6.13, bullet point three "the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery", with regard to the oral medications that confer increased risk of hypoglycaemia, namely repaglinide and sulfonylurea. For increased clarity, and continuity between the findings of the full and short guideline document MSD suggest the following text: (1.6.13) Do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless: • The person is on oral medication (**repaglinide or sulfonylurea**), that may increase their risk of hypoglycaemia while driving or operating machinery The findings of the of the network meta-analysis (NMA) presented in the full guidance document (figure 12, page 184-185) clearly demonstrate an increased hazard of hypoglycaemia for patients treated with repaglinide or sulfonylurea, as both sets of credible intervals **did not** cross the line of significance (HR 1.0). The risk of hypoglycaemia at study end point was statistically significantly greater in patients treated with repaglinide or sulfonylurea compared with placebo; whereas, all other interventions (10 modelled) presented in this NMA were considered non-significant and crossed	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. [new 2015]

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						the line of significance. The T2DM guideline should follow verbatim the wording of 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: <u>Group 1 drivers (car, motorcycle):</u> • 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 • 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	

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						field defect. **(Highlighted text indicates addition/ alteration)** **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 9 July 2015	
188	SH	Newcastle University	NICE	21	General	*1.6.13, bullet 3* While 'driving and operating machinery' can be widely interpreted, most readers will interpolate 'motor vehicles' and 'in factories' with these words. The list of occupations is much wider – tugboat pilots, railway track maintenance staff, surgeons, nursery staff are amongst the many others I have seen and would include here, or rather suggest broader wording such as 'and those in other occupations or situations where hypoglycaemia might put themselves or others at particular risk.'	Thank you for your feedback. The guideline development group considered the phrase adequate in providing guidance on when self-monitoring of blood glucose should be offered.
189	SH	Newcastle University	NICE	21	General	*1.6.15* This is totally weird – all people all the time with type 2 diabetes are at 'a risk of hyperglycaemia', by definition. I think you mean 'are at risk of acute exacerbation of hyperglycaemia and of ketoacidosis during intercurrent illness'. Further	Thank you for your feedback. Recommendation 1.6.15 (NICE short version) has been rephrased to: 1.6.15 Be aware that adults with type 2 diabetes who have acute intercurrent

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						under these circumstances it is not just treatment review that is necessary – 'take necessary diagnostic steps, review need for monitoring, refer, and alter glucose-lowering and other therapies, as necessary'.	illness are at risk of worsening hyperglycaemia. Review treatment as necessary. [new 2015]
167	SH	Merck Sharp & Dohme UK	NICE	22	1 -15	**<u>The benefits and risk of drug treatment</u>** MSD welcome the addition of the drug treatment paragraph in section 1.6.17 within the short guideline document, which describes numerous factors that should be considered by both the clinician and patient when prescribing pharmacological therapy. However, MSD are concerned about how section 1.6.17 will be interpreted by HCPs, and ultimately how all the factors will be considered and applied in clinical practice. Further clarity is required to ensure these considerations are read correctly and implemented consistently across the NHS to minimise variation. It would be logical to assume that these prescribing factors have been listed hierarchically, prioritising the effectiveness of the treatment, safety and licenses above other factors. Therefore, to enable effective implementation and consistency when prescribing these factors should be clearly ranked; see example text below (**Drug treatment; 1.6.17**). In addition the GDG commented "the guideline	Thank you for your feedback. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. The antihyperglycaemic pharmacotherapy recommendations and algorithm were derived following consideration of the clinical and cost effectiveness evidence and guideline development group's clinical experience. The cost effectiveness analyses considered long term outcomes and costs achieved via HbA1c control as well as short term outcomes and drug costs (see appendix F). Recommendations referring to drug cost were made when drugs were found to have sufficiently similar clinical and cost effectiveness. Individualised care does not preclude guidance on clinically and cost-effective treatment options. Newer and more innovative medicines that are not included in guidelines can be evaluated in the NICE

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						assumes that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients", which has been added to page 4 of the short guideline document. To ensure that HCP use a medicine's summary of product characteristics (SPC) when considering pharmacological therapy bullet-points 2 ("MHRA safety warning") and 5 ("license indication") should be updated to include text that refers the reader to a medicines SPC; see example text below (**Drug treatment; 1.6.17**). **Drug treatment** 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. **Base the choice of drug treatment(s) on the factors below in descending order of priority:** • the effectiveness of the drug treatment(s) in terms of metabolic response • **Safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance and medicines Summary of Product Characteristics) and tolerability of the drug treatment(s)** • the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy	technology appraisal process. 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 relevant technology appraisals.

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						• the person's individual preferences and needs • **The licensed indications or combinations available (see medicines Summary of Product Characteristics)** • ~~cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).~~ ***(Highlighted text indicates addition/ alteration)*** Finally, MSD believes the inclusion of "cost" (bullet 6, of section 1.6.17) is inappropriate and therefore, should be removed. In recognition of the challenging financial situation that the NHS faces, it is highly likely that those who are responsible for budgets may solely use "cost" (bullet 6) as a factor to inappropriately control expenditure, disregarding the other relevant factors. The inclusion of this factor has the potential to drive inappropriate prescribing, which could have safety implications and disregards individualised patient care. Furthermore, inappropriate prescribing based on cost alone contradicts three of the five guiding principles (principle: 1, 3 and 4) of the medicines optimisation strategy[1]; runs counter-intuitive of the NHS five year forward plan[2]; and does not take into consideration the ABPI Pharmaceutical Price Regulation Scheme (PPRS) agreement, which allows the NHS greater flexibility when prescribing	

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						innovative branded medicines, for which all costs of prescribing over an agreed threshold are underwritten by the pharmaceutical industry[3]. References: 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 July 2015 2. NHS Five Year Forward View, October 2014. PDF online, http://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf; accessed July 2015 3. ABPI, Understanding the 2014 Pharmaceutical Price Regulation Scheme, January 2014. PDF online, http://www.abpi.org.uk/our-work/policy-parliamentary/Documents/understanding_pprs2014.pdf; accessed July 2015	
118	SH	Diabetes UK	NICE	22	2-15	**Individualising drug treatment** We welcome the recommendation to base choice of drug treatments on, among other considerations, person's individual circumstances, preferences and needs. However, we suggest there should be a clear recommendation for	Thank you for your feedback. It is expected that healthcare professionals would undertake a thorough assessment (including history) and discuss the available options with individuals before deciding the appropriate course of action.

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						clinicians to include in their conversations about drug treatments • the individual targets for the person with diabetes • for those not meeting their targets what else may be going on in their life which may impact on their diabetes management and • agreed appropriate steps to meeting their targets considering the options along the treatment pathway This will give the person the opportunity to be actively involved in their care planning.	
93	SH	AstraZeneca	NICE	22	5	*Lines 5-15 / Algorithm table* **<u>While the full guideline rightly draws attention to the importance of weight in treatment choice, this is not similarly reflected in the short version</u>** **Concern** AstraZeneca is pleased to see that the full guideline now gives detailed consideration to factors that should guide a prescriber in individualising therapy, including: Identification of weight (gain) as a "harm" in the economic models *[page 252 full guideline]*, acknowledgement that in some patients treatment-related weight gain would not be	Thank you for your feedback. The guideline development group (GDG) agreed that to facilitate usability, the list of factors should be concise and coherent. The GDG considered a range of adverse effects including weight and hypoglycaemia.

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						acceptable *[page 223 full guideline]* and broader discussion of the importance of weight management *[page 35 full guideline]* Recognition that change in body weight is important in determining the acceptability of treatment to an individual *[page 250 full guideline]* as medications that result in weight gain negatively impact quality of life, self esteem and treatment compliance [*page 35 and page 197 full guideline]* Consideration of weight as *important* in guiding decision making *[page 196 and 221 full guideline].* General advice that health care professionals tailor treatment approaches to the needs and circumstances of individual patients *[page 15 full guideline]* However, this helpful information is not provided in the short version (which is likely to be the main source used by prescribers). **Recommendation** Include weight alongside other factors (effectiveness, safety, tolerability etc.) both in the generic recommendations on page 22 *[line 5-15 short guideline]* and in the algorithm on page 23 *[short guideline]*. 1. Public Health England, 2014. Adult obesity and type 2 diabetes. Available at: https://www.gov.uk/government/uploads/system/u	

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						ploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf (Accessed July 2015) 2.Glogner 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 3. Ross SA Impact of weight gain on outcomes in type 2 diabetes. Curr Med Res Opin. 2011 Jul;27(7):1431-8.	
94	SH	AstraZeneca	NICE	22	5	*Pages 22-23, Lines 5-15 Algorithm table* **While the full guideline rightly draws attention to the importance of hypoglycaemia risk in treatment choice, this is not similarly reflected in the short version** **Concern** We are pleased to see that the full guideline now gives detailed consideration to factors that should guide a prescriber in individualising therapy, including the following: Advice that health care professionals tailor treatment approached to the needs and circumstances of individual patients *[page 15 full guideline]* Consideration of HbA1c, hypoglycaemic events and adverse events as *critical* in guiding decision	Thank you for your feedback. The guideline development group (GDG) agreed that to facilitate usability, the list of factors should be concise and coherent. The GDG considered a range of adverse effects including weight and hypoglycaemia.

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						making *[page 196 and 221 full guideline]* Clear attention given to the importance of weight management *[page 35 full guideline]*. Identification of hypoglycaemia as a "harm" in the economic models *[page 252 full guideline]* The potential to safely aim for lower HbA1c targets when using treatments not associated with hypoglycaemia *[page 122 full guideline line 31-33; pg 23 algorithm: target for patients for whom metformin is contraindicated]* These recommendations are in line with epidemiologic findings that indicate that patients with hypoglycemia have significantly higher risks of cardiovascular events (hazard ratio 2.0 [95% CI 1.6–2.4]) and microvascular complications (hazard ratio 1.76 [95% CI 1.46–2.11]) (1). Moreover, they reflect the fact patients who experience moderate or worse symptoms of hypoglycemia report poorer adherence to medication (2) and that any form of hypoglycemia is known to have a negative impact on health-related quality of life (3). This helpful information around hypoglycaemia is not provided in the short version (which is likely to be the main source used by prescribers). **Recommendation** Include hypoglycaemia risk alongside other	

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						factors (effectiveness, safety, tolerability etc.) both in the generic recommendations on page 22 *[line 5-15 short guideline]* and in the algorithm on page 23 *[short guideline]*. 1. Zhao Y Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. Diabetes Care 2012;35:1126–1132 2. Walz L Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. Patient Prefer Adherence. 2014 Apr 30;8:593-601. 3. Harris S The effect of hypoglycemia on health-related quality of life: Canadian results from a multinational time trade-off survey. Can J Diabetes. 2014 Feb;38(1):45-52	
32	SH	Aneurin Bevan University Health Board	NICE	22	14	Drugs in the same class can vary regarding safety profile and efficacy in individual patients depending on health status this is a clinical decision, There is concern that DPP4 inhibitors may have different cardiac risk profiles, sulphonylureas have differing half-life and efficacy as well as GLP-1 analogues . It should be emphasised that cost should be considered after the efficacy and safety have been assessed between drugs after a negotiated period of therapy.	Thank you for your feedback. Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) mimetics and sulfonylureas refer to these groups of drugs at a class level because based on the evaluated evidence, the guideline development group was not convinced of the purported material differences between the various preparations. Class recommendations facilitate individualised care.

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45	SH	Primary Care Diabetes Society	NICE	22	14	Drugs in the same class can vary regarding safety profile and efficacy. Therefore advising the lowest acquisition cost of a drug within a class is not appropriate. There is now some concern that DPP4 inhibitors may have different cardiac risk profiles. Sulphonylureas have differing half-lives and efficacy as well as GLP-1 analogues. It should be emphasised that cost should be considered after the efficacy and safety have been assessed even with drugs that are in the same class.	Thank you for your feedback. Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) mimetics and sulfonylureas refer to these groups of drugs at a class level because based on the evaluated evidence, the guideline development group was not convinced of the purported material differences between the various preparations. Class recommendations facilitate individualised care.
96	SH	AstraZeneca	NICE	22	14	*Pages 22-3, Lines 14-5 Algorithm upper box* **<u>Generic guidance around treatment choice is still guided by acquisition cost</u>** **Concern** AstraZeneca recognizes that this draft of the guideline places greater emphasis on individualised care and flexibility in treatment choice than did the previous version. We are concerned, however, that the current draft still highlights drug acquisition cost as a key factor guiding treatment choice. Given the PPRS agreement and NICE's remit, we believe that the guidelines should facilitate appropriate access to innovative treatments for which cost-effectiveness has been demonstrated.	Thank you for your feedback. Recommendation 1.6.17 (NICE short version) provides a list of factors to consider when selecting drug treatments, not only acquisition costs. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy

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						Recommendation Remove the statement that "if two drugs in the same class are appropriate, a prescriber should choose the option with the lowest acquisition cost".	• the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [new 2015]
269	SH	Training, Research and Education for Nurses in Diabetes	NICE	22	14	1.6.17 Drugs in the same class can vary regarding safety profile and efficacy. Therefore, advising the lowest acquisition cost of a drug within a class is not appropriate.There is now some concern that DPP4 inhibitors may have different cardiac risk profiles , sulphonylureas have differing half-lives and efficacy as well as GLP-1 analogues . It should be emphasised that cost should be considered after the efficacy and safety have been assessed between drugs that are being reviewed as the next intervention.	Thank you for your feedback. Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) mimetics and sulfonylureas refer to these groups of drugs at a class level because based on the evaluated evidence, the guideline development group was not convinced of the purported material differences between the various preparations. Class recommendations facilitate individualised care.
156	SH	Leeds North Clinical Commisioning Group	NICE	22	17 -20	This is an important fact to point out which will hopefully lead to more rapid control of symptoms for the patient while stressing the importance of reviewing treatment once the blood glucose is under control again. It is useful that this information is also included in the algorithm.	Thank you for your feedback.
190	SH	Newcastle University	NICE	22	General	*1.6.20* This has to be wrong ['over several months'], as it increases clinical load and results in undertreatment. This is what we used to do in the 1990's. Starting metformin as 'stepped titration	Thank you for your feedback. Recommendation 1.6.20 (NICE short version) states 'over several weeks', not months.

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						over one month until a full therapeutic dose is achieved or a lower tolerated dose established' is much the better practice. There is no strong evidence here but undertreatment from slow dose titration of glucose-lowering agents is well described. The original CG66 wording ' Step up metformin therapy gradually over weeks to minimise risk of gastro-intestinal (GI) side effects.' was better but still perhaps not ideal.	1.6.20 Gradually increase the dose of standard-release metformin over several weeks to minimise the risk of gastrointestinal side effects in adults with type 2 diabetes. [new 2015]
113	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	23	1	The presentation of the algorithm is not fit for purpose. It is extremely wordy and unlikely to be widely referred to in its present format. Alternative guidance such as the EASD/ADA guidance is much more clearly presented. A case can be made for a separate algorithm for the frail elderly who are not served well by this guideline.	Thank you for your feedback. For simplicity, a single A4 page algorithm has been developed which can be adjusted based on individual circumstances such as people who are newly diagnosed or frail elderly. It is not feasible to have individual algorithms for every clinical scenario. It is expected that clinicians would undertake a thorough assessment and consider individual circumstances when discussing the benefits and risks of each treatment option before agreeing the appropriate course of action.
97	SH	AstraZeneca	NICE	23	22	*Page 24 lines 13-16, page 23 & 22-24; Algorithm table first and second intensification box* **<u>Unclear rationale for the order of proposed combinations</u>** **Concern** The rationale for the ordering of proposed	Thank you for your feedback. The order of the treatment options was originally based on the evaluated clinical and cost-effectiveness evidence. However, the treatment options have now been re-ordered alphabetically.

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						combinations at first and second intensification is not clear: the current version inadvertently implies a preference for combinations listed first. **Recommendation** Order options alphabetically.	
89	SH	AstraZeneca	NICE	23	General	*Algorithm table:* **Potential for confusion around the role of SGLT-2 inhibitors: these agents are not clearly included in the algorithm** **Concern** AstraZeneca is glad to see that SGLT-2 inhibitors (SGLT2-i) are incorporated in the revised algorithm: this represents clear progress from the previous version where no guidance around the use of this class of medications was given as they were stated to be "beyond the scope of these guidelines". In the revised draft reference to the SGLT2-i class is restricted to a single footnote. Mentioning, yet apparently de-emphasising, the place of agents in this class has the potential to lead to confusion among prescribers. This is surprising as SGLT2-is have received positive recommendations from NICE in three distinct technology assessments (TA288, TA315 and TA 366).	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also looking into further ways of presenting this information.

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						Recommendation Refer to the SGLT2-i class directly in the boxes providing advice at first and second intensifications, retaining the footnote describing scope, i.e. add: "- metformin and a SGLT-2i" in the first intensification box and: "- metformin, an SU and a SGLT-2i" in the second intensification box	
90	SH	AstraZeneca	NICE (Full)	23 24 (223)	General	*Algorithm table:* **<u>Potential for confusion around the role of GLP-1 receptor agonists: these agents are not included at the first intensification stage and their position at the second intensification stage is unclear</u>** **Concern** At first intensification, we note that in NICE's analysis the combination of metformin and GLP-1 receptor agonist (RA) was shown to be the most effective of all combinations at promoting weight loss *[page 221 full guideline],* suggesting the potential to improve outcomes in patients with high BMI. The guideline contains a statement to this effect, i.e. that a combination of metformin with a GLP-1 mimetic may be effective in reducing HbA1c levels, preventing hypoglycaemic events and promoting weight loss. At the same time, we note the view that this option should not be	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that

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						prescribed routinely given safety and cost-effectiveness safety considerations *[page 223 full guideline].* While we agree that GLP-1 RAs should not be a routine treatment option at first intensification, we believe that completely excluding the possibility of a combination of metformin and GLP-1 RA at the first intensification stage contradicts the broader recommendation that prescribers follow an individualized treatment approach tailored to the needs and circumstances of individual patients *[page 15 full guideline*], especially given the potential for agents in this class to positively impact body weight gain, an issue given a great deal of consideration elsewhere in the guideline. Incidentally, while no further considerations around the long term safety of agents in the GLP-1 RA class are mentioned, we draw attention to the following new data: (i) a 5 year follow-up study with exenatide demonstrating that it is generally well tolerated and offers sustained glycaemic improvement (1) (ii) a cardiovascular outcomes study with lixisenatide confirming that the cardiovascular-safety profile is non-inferior to placebo (2) At second intensification the guideline is unclear as regards the positioning of the GLP-1 RA class:	this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an 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. The GDG noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to

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						the current presentation leaves itself open to two possible interpretations: That GLP-1 RAs are a true option at second intensification, i.e. at parity with triple oral therapy and with insulin That GLP-1 RAs are only an option (in combination with metformin and a sulphonylurea) if triple oral therapy has failed, i.e. tantamount to positioning as "third intensification" Interpretation i) remains consistent with previous NICE guidance, i.e. STA 248. This recognises that GLP-1 RAs can be given with two other drugs i.e. metformin and either a a sulphonylurea or a thiazolidinedione in specific patients (i.e. those uncontrolled with BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or patients that have a BMI lower than 35 kg/m^2, and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities). In the absence of a compelling reason to change position, it would seen sensible to continue to offer the option to combine metformin, a sulphonylurea and a GLP-1 RA at second intensification as an alternative to triple oral therapy. This might be a useful option in, for example, patients with high BMIs and specific	enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.

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						psychological or other medical problems associated with obesity. If this interpretation is indeed what is intended, this is not clear and there is the potential for confusion among prescribers. Interpretation ii) is not consistent with previous guidance and it is unclear why the new guideline recommendations would position the GLP-1 RA class in this way. As well as being at odds with STA 248, interpretation ii) falls out of line with guidance presented elsewhere in the draft guideline. This gives clear recommendations that treatment be individualised to particular patients: specifically, it acknowledges the negative effects of weight gain of medication on patients' quality of life, self esteem and treatment compliance *[pages 15, 5 and 197 full guideline]*. **Recommendation** Present the combination of a GLP-1 RA and another drug (either metformin or a sulphonylurea) as an option in the first intensification box "for selected patients with a high BMI". Clarify the position of GLP-1 RAs at second intensification in line with i), noting that such agents should be considered in preference to insulin (see comment 4). Include the combination of GLP-1 RA with metformin and SU as a choice	

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						positioned above insulin in the list of triple therapies appearing in the second intensification box, and hence as an alternative to triple oral therapy for specific patients (those with BMI ≥ 35 kg/m^2 and specific psychological or other medical problems associated with obesity or patients who have a BMI lower than 35 kg/m^2, and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities). 1 Wysham C, Five-year efficacy and safety data of exenatide once weekly: long-term results from the DURATION-1 randomized clinical trial. Mayo Clin Proc. 2015 Mar;90(3):356-65. 2 Press release from Sanofi-Aventis. Available at: http://en.sanofi.com/NasdaQ_OMX/local/press_releases/sanofi_announces_topline_resul_1904474_19-03-2015!07_00_00.aspx (Accessed July 2015)	
95	SH	AstraZeneca	NICE	23	General	*Pages 23-4, Footnotes 3 and 1* **Prominent place given to pioglitazone without clear reference to potential adverse events and cautions for use in the elderly** **Concern** AstraZeneca is pleased to see that the positions of pioglitazone and repaglinide in the treatment	Thank you for your feedback. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: • heart failure or history of heart failure ,

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						algorithm have been revised. Given that the use of pioglitazone is associated with a number of potential safety concerns (especially in the elderly) it would seem important that attention should be drawn to these such that a informed prescribing decisions can be made (1,2). In the current draft a footnote warns prescribers to exercise particular caution if those at high risk of the adverse events, but does not specify what these are or give any note of caution around the use of this agent in the elderly. **Recommendation** Change the footnote on pioglitazone to include reference to the major cautions listed in pioglitazone's Summary of Product Characteristics, i.e. "concerns around bone fractures, worsening of heart failure, weight gain and use in the elderly" (2). 1. Actos Summary of Product Characteristics https://www.medicines.org.uk/emc/medicine/4236. (Accessed July 2015) 2. Kung J, Thiazolidinedione safety. Expert Opin Drug Saf 2012;11:565–579	• hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015] A footnote on the safety alerts for pioglitazone was added, and a note to exercise particular caution if the person is at high risk of the adverse effects of this drug. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action.
98	SH	AstraZeneca	NICE	23	General	*Algorithm table: A) Box insulin treatment B)footnotes C)footnotes* **Technical suggestions to improve the clarity of the treatment algorithm table**	Thank you for your feedback. The text has been amended to "Only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary

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						Concern The following advice appears in the treatment algorithm table: "Only offer insulin and a GLP-1 mimetic with specialist care advice and ongoing support' could be misleading and give the impression that GLP-1 RAs should only ever be used with specialist advice (rather than specifically in the case where these agents are used in combination with insulin). **Recommendation** Re-write the advice as follows: "Only offer insulin and a GLP-1 mimetic in combination with specialist advice and ongoing support". Note that similar text already appears in the short guideline. **Concern** While diabetologists and GPs with a specialist interest in diabetes are given as examples of health care professionals able to provide specialist care, no mention is made of diabetes specialist nurses. Naturally this expert group plays a key part in specialist diabetes care provision in the UK. **Recommendation** Include Diabetes Specialist Nurses throughout the document when referring to examples of health	team", where the consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care. Footnotes have been changed using the alphabet and are ordered in sequence of appearance.

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						care professionals able to provide specialist care. **Concern** In the treatment algorithm table the "2" in "m^2" could be confused for a reference to footnote 2 **Recommendation** Use symbols such as "*" and "#" to refer to footnotes **Concern** References and footnotes are not presented in the order in which they are mentioned in the algorithm. This has the potential to cause confusion **Recommendation** Re-order references and footnotes such that they appear in the order in which they are presented.	
129	SH	Diabetes Reference Group Conwy and Denbighshire	NICE	23	General	We thought that this "algorithm" will be very useful to busy GPs.	Thank you for your feedback.
157	SH	Leeds North Clinical Commisioning Group	NICE	23	General	*Algorithm:* Much better that it's all on one page, which makes it easier for prescribers to view and print. This algorithm is much clearer to follow that the ones in the first draft! You mention the need for a patient centred approach and individualising target	Thank you for your feedback. The guideline development group (GDG) recognises in the guideline that multiple factors need to be considered when setting HbA1c target levels and has developed recommendations to facilitate individualised

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						HbA1c levels throughout the guidance, however this isn't reflected in the algorithm which appears to be very target driven. We think this will lead prescribers (who perhaps won't have read the whole document) to strive to achieve the target HbA1c levels contained in the algorithm. SGLT-2 inhibitors are noticeable by their absence in the algorithm, yet they are referred to in footnote 3 at the bottom. This is confusing and leads to uncertainty to their place in therapy. It also requires prescribers to have to go and read three separate TAs to try and work out what your recommendations are. This is very disjointed, potentially leading to confusion and misinterpretation. Repaglinide is still given too much prominence; we feel many prescribers will ignore it as it's only useful in such a narrow range of patients.	care (for example, see recommendations 1.6.5 and 1.6.9 in the NICE short version). However, the GDG considered it important to provide guidance on target HbA1c levels for non-specialists in particular, who would then be able to discuss with individuals, appropriate target and intensification HbA1c levels. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to

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							highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
205	SH	Novo Nordisk Ltd	NICE	23	General	*Short page 23 algorithm & page 25 line 1 / Full page 257 line 23 & apge 14 algorithm* 'Metformin contraindicated or not tolerated' part of algorithm, Section 1.6.25 We commend NICE for inclusion of the GLP-1 mimetic class into the algorithm explicitly as indeed clinicians and other healthcare professionals should see clearly that this is a valuable treatment option for patients with type 2 diabetes. However it seems an oversight that GLP-1mimetics are missing from the "metformin contraindicated and not tolerated" part of the pathway in the algorithm. We would suggest an amendment such that they are included as an option in the first intensification box as was previously advised by NICE in TA203[1] section 4.22, i.e. liraglutide in dual therapy should be recommended as an option for the treatment of people with type 2 diabetes, if the person is intolerant of either metformin or a sulphonylurea, or treatment with metformin or a sulphonylurea is	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations have been made.

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						contraindicated. References: 1. National Institute for Health and Care Excellence (NICE). Liraglutide for the treatment of type 2 diabetes mellitus. NICE technology appraisal guidance TA203. October 2010. Available at: http://www.nice.org.uk/guidance/ta203 (Accessed July 2015)	
206	SH	Novo Nordisk Ltd	NICE	23	General	*Short page 23 algorithm & page 28 after lines 2 or 26* *Full page 259 after line 34, page 260 after line 10, page 14 algorithm & page 253 3rd paragraph* <u>'Insulin-based treatment' part of algorithm - After Section 1.6.33 or 1.6.34</u> Novo Nordisk requests NICE to consider insulin degludec as an option after failure of insulin detemir or insulin glargine, and include as part of the Type 2 treatment algorithm. Insulin degludec has been available in the UK since February 2014 and has proven its benefit in clinical practice. Several UK HCPs have published their experience with insulin degludec in type 1 and type 2 diabetes patients[1-6], demonstrating improvements in glycaemic control and	Thank you for your feedback. The recommendations in this guideline are based on evaluations of clinical and cost-effectiveness evidence, and not only the available licensed options. It is unclear the limitations being referred to in the inclusion/exclusion of studies from the systematic review that may have particularly disadvantaged insulin degludec. The cost-effectiveness analyses considered long-term outcomes and costs achieved via HbA1c control as well as short-term outcomes and drug costs (see appendix F). Recommendations referring to drug cost were made when drugs were found to have sufficiently similar clinical and cost-effectiveness.

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						hypoglycaemia in certain patients. It is relevant to include in the algorithm that insulin degludec in diabetes patients already using an insulin analogue and experiencing problems with recurrent hypoglycaemia, poor compliance or need of flexibility in dosing may benefit from insulin degludec. Insulin pumps are often considered in these patients so Novo Nordisk do not feel that it is justified to omit insulin degludec from the algorithm on the basis of cost in terms of the patient population referred to. The availability of 160IU pen also allows patients with high dose requirements to administer the required daily dose of insulin degludec as a single injection[7]. It should be noted also that the strong evidence that the GDG is dependent on (p253 of the full guidelines, third paragraph) i.e. the economic modelling deeming insulin degludec as not cost-effective, was not without limitations. Limitations in including/excluding clinical studies from the systematic review and so relying upon a small number of randomized controlled trials for individual therapies only, followed by the complexity of the network meta-analysis which applied the same assumptions for fixed dose and titratable (i.e. insulin) medications (frequency, severity and timing of hypoglycaemia events; weight reduction effects and therapy intensification thresholds), and has led to	Individualised care does not preclude guidance on clinically and cost-effective treatment options.

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						homogenizing the health outcomes across the different treatment options. Hence the evidence synthesis and health economic approach appears to be counter-intuitive, potentially leading to unclear results and guideline recommendations that appear primarily acquisition cost focused – overall they fail to provide clear advice on the value for money of different approaches to achieving diabetes control in routine clinical practice. There are a significant number of healthcare professionals currently using insulin degludec in specific patient populations and documenting clinical benefits[1-6]. It is important that NICE clinical guidelines reflect real life clinical practice and that these guidelines acknowledge the patients who need another step in the algorithm to have the option of insulin degludec. References: 1. Acharya J, et al. Insulin degludec, an alternative to insulin U500, in severe insulin resistance. Association of British Clinical Diabetologists Autumn meeting, London 2014 2. Kurera I et al. Review of Clinical use of insulin degludec as a basal insulin. Poster presented at the Diabetes UK Professional Conference, London, 2015	

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						3. Robinson et al - Clinician reported insights of insulin degludec across five European countries - Diabetes UK Professional Conference, London, 2015 4. Dar et al - Effectiveness of insulin degludec in Type 1 diabetes - Diabetes UK Professional Conference, London, 2015 5. Evans et al - Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practice – a case based evaluation. Journal of Medical Economics, 2014. 6. Lena Landstedt-Hallin. Changes in HbA1c, insulin dose and incidence of hypoglycaemia in patients with type 1 diabetes after switching to insulin degludec in an outpatient setting: an observational study. Current Medical Research & Opinion. Doi: 10.1185/03007995.2015.1058252. 7. Hemmingsen H, Diabetes Technol Ther 2011; 13:1207–1211	
224	SH	Sanofi	NICE	23	General	Elsewhere in the guideline GLP-1 RAs are recommended as an option in combination with basal insulin. This is currently not reflected in the treatment algorithm, where GLP-1 RAs appear to be recommended only in combination with metformin and sulphonylurea. It would be helpful to provide clarity to prescribers on the use of GLP-1 RAs in combination with basal insulin in the algorithm. It may also be helpful to clinicians to provide guidance on the use of GLP-1 RAs in combination	Thank you for your feedback. GLP-1 mimetics in combination with insulin appear in the algorithm in the insulin-based treatments grey box.

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						with both basal insulin and sulphonylurea due to the potential additive effect on hypoglycaemia from the three agents: In the summary of product characteristics for GLP-1 RA treatments there is a recommendation to consider reducing the dose of the sulphonylurea and/or basal insulin when a GLP-1 RA is initiated.	
128	SH	Diabetes Reference Group Conwy and Denbighshire	NICE	24	1	We are pleased to see the inclusion of a trial of modified release metformin, where the standard release version is not tolerated.	Thank you for your feedback.
119	SH	Diabetes UK	NICE	24	3	We welcome the clear guidance on when modified-release Metformin should be considered	Thank you for your feedback. Recommendation 1.6.21 (NICE short version) provides guidance on when modified-release metformin should be considered. 1.6.21 If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. [new 2015]
121	SH	Diabetes UK	NICE	24	17 -21	**First intensification** We suggest adding 'If metformin has failed to achieve agreed blood glucose control, ideally the choice of second or third line therapy should be agreed between the clinician and the person with diabetes, choosing the most appropriate therapy for them, as recommended in the EASD/ADA	Thank you for your feedback. It is expected that clinicians would discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action. In addition, recommendation 1.6.17 (NICE short version) provides a list of factors to

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						guidance'.	consider when selecting drug treatments. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy • the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [new 2015]
34	SH	Aneurin Bevan University Health Board	NICE	24	22	A comment should be made regarding urinalysis to screen for haematuria prior to initiating Pioglitazone as a safety feature regarding concerns of bladder cancer.	Thank you for your feedback. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following:

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							• heart failure or history of heart failure , • hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015] It is expected that healthcare professionals would undertake the necessary assessments to ensure that individuals are not contraindicated to medicines prior to prescribing.
47	SH	Primary Care Diabetes Society	NICE	24	22	As a safety feature regarding the concern surrounding incidence of bladder cancer, comment should be made regarding urinalysis to screen for haematuria prior to initiating Pioglitazone.	Thank you for your feedback. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: • heart failure or history of heart failure , • hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015] It is expected that healthcare professionals would undertake the necessary assessments to ensure that individuals are

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							not contraindicated to medicines prior to prescribing.
100	SH	Central Manchester University Hospitals NHSFT	NICE	24 (23)	22 (Table)	We are concerned that the layout of the flow chart and text gives the impression that Metformin + pioglitazone is first choice for dual therapy	Thank you for your feedback. The order of the treatment options was originally based on the evaluated clinical and cost-effectiveness evidence. However, the treatment options have now been re-ordered alphabetically.
271	SH	Training, Research and Education for Nurses in Diabetes	NICE	24	22	1.6.24 A comment should be made regarding urinalysis to screen for haematuria prior to initiating Pioglitazone as a safety feature regarding concerns of bladder cancer.	Thank you for your feedback. A new recommendation has been added 1.6.24 (NICE short version) that outlines the contraindications stated in the summary of product characteristics: 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following: • heart failure or history of heart failure , • hepatic impairment • diabetic ketoacidosis, • current, or a history of, bladder cancer • uninvestigated macroscopic haematuria. [new 2015] It is expected that healthcare professionals would undertake the necessary assessments to ensure that individuals are not contraindicated to medicines prior to prescribing.
33	SH	Aneurin Bevan	NICE	24	24	There should be more emphasis that SGLT-2 inhibitors could be used at this stage if appropriate	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on

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		University Health Board				to biochemical and health co-morbidities. This will bring NICE guideline up to date with other National Guidance. Not having SGLT-2 placed officially at this stage could mean that use could be reduced in appropriate patients.	sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
46	SH	Primary Care Diabetes Society	NICE	24	24	There should be more emphasis that SGLT-2 inhibitors could be used at this stage if appropriate. This will bring NICE guideline up to date with other National Guidelines. Not having SGLT-2 placed officially at this stage will mean that their use could be reduced in appropriate patients, unless they are seen in a specialist clinic.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
270	SH	Training, Research	NICE	24	24	1.6.24 There should be more emphasis that SGLT-2	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on

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		and Education for Nurses in Diabetes				inhibitors could be used at this stage if appropriate . This will bring NICE guideline up to date with other National and Global Guidance . Not having SGLT-2 placed officially at this stage will mean that their use could be reduced in appropriate patients, if not seen in a specialist clinic. This is more expensive as would increase hospital outpatients attendances – this is against the Govt. agenda.	sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
99	SH	Boehringer Ingelheim	NICE	24	General	The Alliance welcome the inclusion of empagliflozin in the update, which now provides the audience with reference to the complete class of SGLT2 inhibitors. The overall guideline recognises the importance of the SGLT2 inhibitor class in the main body of the guideline, however, the reference to the class still lies in the *footer* of the figure on page 24. The Alliance is concerned that this positioning will limit the audience's awareness of the class at the first intensification stage. The overall intention of the update is to present prescribers with all appropriate options to enable them to effectively treat their type 2 diabetes patients. All three members of the SGLT2i class with marketing authorisation now have TAG issued by NICE. The Alliance asks that the class be included within the main scheme and	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.

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						be added to the grey box.	
114	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	24	General	'Prescribe metformin with caution for those at risk sudden deterioration in kidney function' This is an excessively cautious recommendation in the light of the minimal evidence of risk of harm from metformin with deteriorating renal function. Much more important to be cautious about ACE inhibitors and other agents which can cause AKI during intercurrent illness (see comment 4)	Thank you for your feedback. This caution is in line with the guidance provided in the summary of products characteristics for metformin.
120	SH	Diabetes UK	NICE	24	General	*Section 1.6.24* **Initial drug treatment** We are concerned that repaglinide is still being considered in view of the fact that repaglinide is mostly taken three times a day which is likely to substantially increase non-adherence. There is also 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.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
149	SH	London Diabetes Strategic Clinical Network &	NICE	24	General	1.6.21 We welcome the clear guidance on when modified-release Metformin should be considered	Thank you for your feedback.

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		Health Innovation Network (joint response)					
150	SH	London Diabetes Strategic Clinical Network & Health Innovation Network (joint response)	NICE	24	General	1.6.23 **Initial drug treatment** We welcome the fact that equal weighting has been given to DPP-4 inhibitors, repaglinide, sulfonylurea and pioglitazone when metformin is contraindicated or not tolerated.	Thank you for your feedback. Based on the evaluated evidence, for people who are contraindicated or intolerant of metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone and sulfonylureas have been recommended as equal options. These options facilitate choice and individualised care based on evidence. A footnote has been added to this recommendation to highlight that there is clinical and cost-effectiveness evidence for the use of repaglinide, along with no available licensed non-metformin-based combinations for drug intensification.
151	SH	London Diabetes Strategic Clinical Network & Health Innovation Network (joint response)	NICE	24	General	1.6.24 **First intensification of drug treatment** It is good that equal weighting has been given to DPP-4 inhibitors, sulfonylurea and pioglitazone as options to be consider for dual therapy with metformin. However, SGLT-2 should be added in the main guidelines as an option rather than a cross-reference to the technology appraisals. We find it unhelpful to have partially updated guidelines with links to other external documents, especially so when that strategy is avoidable in	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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

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						this instance. It will be more practical to have the guidance on SGLT-2 fully incorporated, and readily accessible, otherwise we are concerned that this aspect of the guidelines risks being overlooked.	diabetes and the technology appraisals. NICE is also exploring different ways of presenting this information.
191	SH	Newcastle University	NICE	25	8	*Page 25 lines 8-13; Page 26 lines 26-30; footnote to algorithm* It is good to see the NICE management problem with SGLT2b's being addressed in some way, though it is still a pity that an algorithm will be published that clinicians will know to be out-of-date and not applicable to their practice after 2014. Can nothing sensible be done here to rescue the money spent on the current revision?	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
35	SH	Aneurin Bevan University Health Board	NICE	25	15	The substitution of a GLP-1 analogue for a DPP4-inhibitor, should be considered if patients have >BMI and are using Metformin and a DPP4-inhibitor, to add a sulphonylurea or Pioglitazone that could cause further weight gain is counter productive.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, 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 mimetic (GLP-1) may be effective in reducing HbA1c levels

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							in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
48	SH	Primary Care Diabetes Society	NICE	25	15	The substitution of a GLP-1 analogue for a DPP4-inhibitor, should be considered if patients have weight issues and are on Metformin and a DPP4-inhibitor, rather than to add a sulphonylurea or Pioglitazone that could cause further weight gain.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, 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 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and

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							promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
272	SH	Training, Research and Education for Nurses in Diabetes	NICE	25	15	1.6.26 The substitution of a GLP-1 analogue for a DPP4-inhibitor, should be considered if patients have weight issues and are on Metformin and a DPP4-inhibitor , rather than to add a sulphonylurea or Pioglitazone that could cause further weight gain.	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, 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 mimetic (GLP-1) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with

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							the use of GLP-1s and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option.
225	SH	Sanofi	NICE	25	24	*NICE page 25 lines 24-26 and page 26 lines 1-2 (and potentially relevant to algorithm on page 23)* In TA203 (Liraglutide for the treatment of type 2 diabetes mellitus) NICE concluded that "taking into account the lack of clinical trial evidence showing a significant benefit from increasing the liraglutide dose from 1.2 mg to 1.8 mg, the widely varying ICERs and the uncertainty in the economic analysis, the Committee was unable to recommend liraglutide 1.8 mg for the treatment of type 2 diabetes." There is no reference in the new guideline to the lack of a recommendation for liraglutide at the 1.8mg dose, and since TA203 will be effectively superseded/replaced by the new guideline in Type 2 diabetes, the new guideline implicitly endorses the use of a medicine at a	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the guideline development group was not convinced of the purported material differences between the various preparations.

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						dose which has been shown not to meet NICE's criteria for clinical and cost effectiveness. The omission of this recommendation contrasts with NICE's efforts elsewhere in the guideline to ensure value for money for the NHS, e.g. through the use of GLP-1 stopping rules and the use where appropriate of the lowest acquisition cost medicine.	
152	SH	London Diabetes Strategic Clinical Network & Health Innovation Network (joint response)	NICE	25	General	1.6.25 **First intensification of drug treatment** The options of using SGLT-2 with other medications as dual therapy when metformin is contraindicated or not tolerated should be fully incorporated into the guidelines rather than cross-referencing to technology appraisals. We find it unhelpful to have partially updated guidelines with links to other external documents, especially so when that strategy is avoidable in this instance. It will be more practical to have the guidance on SGLT-2 fully incorporated, and readily accessible, otherwise we are concerned that this aspect of the guidelines risks being overlooked.	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. 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 the technology appraisals. NICE is also exploring different ways of presenting this information.
153	SH	London Diabetes Strategic Clinical Network & Health Innovation	NICE	25	General	1.6.26 **Second intensification of drug treatment** The options for triple therapy should be expanded to fully incorporate SGLT-2 in the main guidelines as an option rather than a cross-reference to the technology appraisals. We find it unhelpful to have partially updated guidelines with links to other	Thank you for your feedback. Cross-referral to NICE technology appraisal guidance on sodium–glucose cotransporter 2 (SGLT-2) inhibitors have been integrated in the algorithm for use at first and second intensification. NICE anticipates that the majority of healthcare professionals will

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		Network (joint response)				external documents, especially so when that strategy is avoidable in this instance. It will be more practical to have the guidance on SGLT-2 fully incorporated, and readily accessible, otherwise we are concerned that this aspect of the guidelines risks being overlooked.	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 the technology appraisals. NICE is also exploring different ways of presenting this information.
175	SH	National Diabetes Nurse Consultant Group	NICE	25	General	*1.6.25 and 1.6.26* Response to second and third line therapy should be assessed and stopped if no impact.	Thank you for your feedback. Recommendation 1.1.1 (NICE short version) recommends "Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective."
36	SH	Aneurin Bevan University Health Board	NICE	26	1	If a GLP-1 analogue is added into a combination with a sulphonylurea. A caution to consider reducing the dose of the sulphonylurea and increased frequency of blood glucose monitoring due to increase risk of hypoglycaemia.	Thank you for your feedback. It is expected that clinicians would undertake a thorough assessment and discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action.
49	SH	Primary Care Diabetes Society	NICE	26	1	If a GLP-1 receptor analogue is added into a combination with a sulphonylurea, consideration should be on reducing the dose of the sulphonylurea and increased frequency of blood glucose monitoring due to increased risk of hypoglycaemia	Thank you for your feedback. It is expected that clinicians would undertake a thorough assessment and discuss the benefits and risks of each treatment option with individuals before deciding the appropriate course of action, including changes to dosages.
273	SH	Training, Research and	NICE	26	1	1.6.27 If a GLP-1 analogue is added into a combination with a sulphonylurea , consideration should be on	Thank you for your feedback. It is expected that clinicians would undertake a thorough assessment and discuss the benefits and

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		Education for Nurses in Diabetes				reducing the dose of the sulphonylurea, and increased frequency of blood glucose monitoring due to increase risk of hypoglycaemia	risks of each treatment option with individuals before deciding the appropriate course of action, including changes to dosages.
160	SH	Lilly UK	NICE	26	37	We are concerned that the body mass index (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 clinical justification for restricting the use of GLP-1 RAs to patients above a certain BMI.	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s

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							may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
204	SH	Novo Nordisk Ltd	NICE	26	3	***Short page 26 line 3 & page 23 algorithm / Full page 258 line 19 & page 14 algorithm*** **Second intensification of drug treatment. Section 1.6.27: BMI restriction of 35 is arbitrary and not based on clinical evidence** It is essential that clinicians and healthcare professionals are informed of the evidence behind the BMI restriction recommendation of 35kg/m^2 as this does not seem to be supported by the current evidence. Evidence for liraglutide in the LEAD[1-6] (Liraglutide Effect and Action in Diabetes) randomised-controlled trial programme has in addition to patients with a BMI >35 also shown cost-effectiveness consistently in patients with a BMI ≤35 as well as patients with BMI from 30-35 (and in some cases BMI <30).	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). All data from the technology appraisals meeting the review's selection criteria were included. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health

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						It seems that GDG perception is based on evidence from CG87 but has overlooked evidence from TA203[7] and TA248[8], which would have further highlighted the fact that GLP-1 mimetics are cost-effective in patients with BMI <35. **References:** 1. Russell-Jones D, Vaag A, Schmitz O, et al. on behalf of the LEAD-5 (Liraglutide Effect and Action in Diabetes 5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus: a randomised controlled trial (LEAD-5). Diabetologia 2009;52:2046–55. 2. Zinman B, Gerich J, Buse JB, et al. LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4). Diabetes Care 2009;32:1224–30. 3. Nauck MA, Frid A, Hermansen K, et al. LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin in type 2 diabetes. Diabetes Care 2009;32:84–90. 4. Marre M, Shaw J, Brandle M, et al. LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26	economic modelling. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.

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						weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1). Diabet Med 2009;26:268–78. 5. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin in patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010;375:1447–56 6. Buse JB, Rosenstock J, Sesti G, et al. LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39–47. 7. National Institute for Health and Care Excellence (NICE). Liraglutide for the treatment of type 2 diabetes mellitus. NICE technology appraisal guidance TA203. October 2010. Available at: http://www.nice.org.uk/guidance/ta203 (Accessed July 2015) 8. National Institute for Health and Care Excellence (NICE). Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. NICE technology appraisal 248 (2012). Available at: http://www.nice.org.uk/guidance/ta248 (Accessed	

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						July 2015)	
37	SH	Aneurin Bevan University Health Board	NICE	26	12	The stop criteria should be altered to either a 3% weight loss **OR** a reduction in HbA1c of 1% at 6 months. Studies have shown that only 24% of patients are likely to achieve these current criteria but 46% will be able to achieve one of these targets. If the GLP-1 is stopped , the patient is likely to undergo reversal of improvements . ***Hall GC. Et.al. Diabet Med.2013Jun;30(6):681-6*** Following the guidelines suggesting the lowest acquisition cost GLP-1 analogue to be used as first line therapy, only the shorter duration therapies will be prescribed. Before stopping the GLP-1 analogue as a class there should be a comment to suggest a trial of a longer acting analogue.	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels

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							and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the GDG was not convinced of the purported material differences between the various preparations. Recommendation 1.6.17 (NICE short version) states that "if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost".
50	SH	Primary Care Diabetes Society	NICE	26	12	The stop criteria should be altered to either a 3% weight loss **OR** a reduction in HbA1c of 1% at 6 months. Studies have shown that only 24% of patients are likely to achieve this current dual criteria but 46% will be able to achieve one of these targets. If the GLP-1receptor analogue is stopped, the patient is likely to undergo reversal of improvements . ***Hall GC. Et.al. Diabet Med.2013Jun;30(6):681-6***	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were

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						GLP-1 receptor analogues have different efficacy. If clinicians follow the draft guideline ,it suggests that the lowest acquisition cost GLP-1 receptor analogue be used. This will mean that only the short duration therapies will be prescribed (short acting GLP-1 receptor analogues are likely only to manage prandial glycaemic changes, whilst those of longer duration have been shown to influence both prandial and fasting glycaemic levels. Before stopping the GLP-1 receptor analogue as a class there should be a comment to suggest a trial of a longer acting analogue.	also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s)

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							refer to these drugs at a class level because based on the evaluated evidence, the GDG was not convinced of the purported material differences between the various preparations. Recommendation 1.6.17 (NICE short version) states that "if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost".
115	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	26	12	'Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in6 months). ' This recommendation represents poor guidance which conflicts with Nice guidance on individualised patient goal centred care. The SIGN guidance on this is much more practical. Some patients get very large improvements in glycaemic control and as a consequence do not loose or gain a small amount of weight. Likewise a patient who gets a very large weight loss but who does not get any change in glycaemic control should not be denied the opportunity to continue on aglp1 as glycaemic control can be addressed in other ways.Ref GLP1receptoragonists in type 2 diabetes - NICE guidelines versus clinical practice *Br J Diabetes Vasc Dis* 2014;14:52-59	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG

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							agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
125	SH	Diabetes UK	NICE	26	12-15	**Continuing with GLP-1 memetic therapy** We are concerned that the current recommendation to only continue GLP-1 memetic therapy if the person with Type 2 diabetes has had both a reduction in HbA1c of at least 11mmol/mol and a weight loss of at least 3% in 6 months seems to disregard the important benefits of achieving either of these targets on its own. Given that GLP-1 is only considered for those who	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had

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						meet a strict criteria, achieving either the HbA1c reduction or the stipulated weight loss should be sufficient motivation to continue on the medication beyond 6months. We suggest rewording this section to read: *Only continue GLP-1 mimetic therapy if the person with Type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c **and/or** a weight loss of at least 3% of initial body weight in 6 months).* Failure to make such changes to the recommendation could lead to some people being taken off the medication in spite of clear evidence of benefiting.	better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack

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							of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
162	SH	Lilly UK	NICE	26	12	The continuation rules for the GLP-1 RAs which include targets for both glycated haemoglobin (HbA1c) *and* weight have been retained. We still believe that the 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. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority

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							groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
203	SH	Novo Nordisk Ltd	NICE	26	12	*Short page 26 line 12 / Full page 21 line 27 & page 253 4th paragraph* Section 1.6.28 short guideline and Section 1.5: 'Stopping rules' It should be noted that the recommendation of both the HbA_{1c} and BMI (Body Mass Index) benefit to be met is inappropriate – the recommendation should be that of HbA_{1c} without the stopping rule for weight loss. Anti-diabetes medications are licensed for improving glycaemic control and not reducing weight. Even though reducing BMI as a supporting benefit certainly has a role to play in improving diabetes care, lowering of HbA_{1c} should remain the primary objective.	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were

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						Furthermore, all therapies for diabetes treatment, no matter the acquisition cost should be subject to such assessment after a set time to ensure the effectiveness is adequate in driving positive HbA_{1c} outcomes for patients. It is inappropriate for the Guideline Development Group (GDG) on behalf of NICE to advise focusing 'stopping rules' on GLP-1 (Glucagon-like peptide-1) mimetics alone and not all medications when there is a lack of evidence behind the 'stopping rules' as noted in Section 2.1, p34 of the short guidelines (Section 1.6, p28 (line 16) and Section 8.4.18, p261 (line 26) of full guidelines). There is no evidence that GLP-1 mimetics have a particularly high level of non-responders or lack of efficacy compared to other medicines – in fact there is considerable published clinical and cost-effectiveness evidence supporting these medicines. It seems that the GDG have based this on their own insights rather than published evidence; simply referring to GLP-1 mimetics as high cost drugs on page 253 of the full guideline (fourth paragraph) is not sufficient to exercise 'stopping rules' on this class of medicines only. All new branded anti-diabetes drugs can be thought of as high cost compared to generic metformin and sulphonylureas. Hence we would request this recommendation (1.6.28) is removed, or applied to all medicines to ensure consistency.	also shown to be not cost effective in the health economic modelling. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. The GDG noted the high

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							costs of GLP-1s 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 GDG 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 1.1.1 (NICE short version) recommends "Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective."
226	SH	Sanofi	NICE	26	12-15	Sanofi supports the use of stopping rules for GLP-1 RAs. We agree that medicines should only continue to be used where they are providing a clinical benefit and that ineffective treatments should be discontinued. We also recognise the cost pressures on the NHS which creates a financial imperative to avoid wasting resource by ineffective therapy. However, it is critical that stopping rules strike the right balance ensuring patients deriving real clinical benefit from their treatment do not have their effective treatment stopped unnecessarily. We believe that the current GLP-1 RA stopping criteria do not strike the right balance and that they risk patients being unnecessarily taken off an	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the

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						effective treatment, so we urge NICE to reconsider this part of the guideline. The Association of British Clinical Diabetologists (ABCD) Nationwide Exenatide and Liraglutide Audits reviewed patients taking GLP-1 RAs in routine clinical practice. They found that a large proportion of patients achieve reductions in both HbA_{1c} and body weight (60.1% of exenatide patients and 59.3% of liraglutide patients) but only 28.6% and 25% of patients on each treatment respectively would be eligible to remain on treatment under the current combined outcome criteria. Therefore a large proportion of patients who achieve a clinically relevant benefit from treatment would have their treatment stopped and an alternative, possibly less effective, therapy instigated. The current stopping criteria, an 11 mmol/mol (1%) reduction in HbA_{1c} AND 3% reduction in initial body weight, is one way to define effectiveness of a GLP-1 RA, but this one-size-fits-all approach disadvantages various groups of patients, such as: • Patients achieving a large HbA_{1c} reduction (e.g. 22 mmol/mol (2%)) but a more modest weight reduction (e.g. 2.5%) • Patients achieving a large weight reduction (e.g. 8%) but a more modest	health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available

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						HbA_{1c} reduction (e.g. 9 mmol/mol (0.8%)) • Patients initiated onto a GLP-1 RA with a lower baseline HbA_{1c} (e.g. 51 mmol/mol (7.8%)) o Such patients are less likely to achieve a large HbA_{1c} reduction, but are still brought to within their target glycaemic range while achieving weight loss and preventing disease progression • Patients taking a GLP-1 RA in combination with insulin o Such patients are typically difficult to treat and are less likely to achieve a 3% weight loss because of the weight-increasing effect of insulin. Maintaining weight neutrality in combination with a reduction in HbA_{1c} would be regarded as an effective treatment and a desirable outcome A great emphasis has been placed throughout the new guideline on individualisation of treatment, as mandated in the NHS Constitution for England. We believe this individualised approach is not sufficiently reflected in the GLP-1 RA stopping rules, where the same clinical response is required of all patients in order to continue therapy, regardless of individual baseline	evidence with a cut off search date of June 2014, and not only the available licensed combinations. Individualised care does not preclude guidance on clinically and cost-effective treatment options.

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						characteristics, comorbidities, concomitant medication etc. It is well documented that patients initiated onto glucose-lowering therapy at a high HbA_{1c} achieve greater reductions in HbA_{1c} than those initiated at lower starting levels. If patients are treated according to the NICE algorithm and are initiated onto a GLP-1 RA as soon as HbA_{1c} reaches 58 mmol/mol (7.5%), they are less likely to achieve an 11 mmol/mol (1%) reduction in HbA_{1c} than patients managed less intensively and initiated with a higher starting HbA_{1c}, and are thus disadvantaged by the current stopping rules. Both patients could achieve clinically meaningful reductions in HbA_{1c} and attain their target HbA_{1c} of 53 mmol/mol (7.0%) but the patient treated according to the algorithm would be required to stop their GLP-1 RA, potentially requiring escalation to insulin therapy which is recognised as causing weight gain, while the less-intensively managed patient, now with the same good level of glycaemic control, could continue treatment. Thus patients managed according to the proposed NICE guideline may be subject to illogical and confusing changes in therapy. Rather than providing logical and clear guidance for therapy the proposed guideline is in danger of increasing confusion and may have a negative impact on	

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						patient care and outcomes for some individuals. In response to stakeholder comments in the first consultation on the draft Type 2 guideline, NICE state that '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.' When CG87 was published the use of GLP-1 RAs in combination with basal insulin was outside their licence because of a lack of published evidence at that time, so stopping rules were based on evidence of GLP-1 RAs used in combination with OADs only. Trials have now been conducted and published in this indication and the majority of GLP-1 RAs now have a licence to be used in combination with basal insulin and are widely used in this manner. Therefore we believe that the stopping rules for patients taking GLP-1 RAs in combination with basal insulin should be revised and based on the available evidence on this treatment combination. It has been established in numerous clinical trials that the additive effect of a GLP-1 RA and basal insulin results in a significant reduction in HbA_{1c}. Insulin is known to cause weight gain but the addition of a GLP-1 RA has been demonstrated to either neutralise or reverse this weight gain, in patients likely otherwise to continue to gain	

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						weight. The expectation of a 3% reduction in body weight is less reasonable in such patients, but the cessation of treatment with GLP-1 RA is likely to result in further weight gain and increase in insulin dose. A change would be needed to the GLP-1 RA stopping rules in order to make them compatible with the use of GLP-1 RAs in combination with basal insulin. In light of these points we urge NICE to reconsider how best to determine the effectiveness of GLP-1 RA treatment and to revise the current GLP-1 RA stopping rules. We believe that the principle of individualisation (of treatment and targets) should be extended to the stopping criteria for GLP-1 RA patients, and stopping criteria should be set on an individual basis, taking into consideration the patient's baseline characteristics, comorbidities and concomitant medication. This would ensure that targets and stopping rules are appropriate for all patients.	
274	SH	Training, Research and Education for Nurses in Diabetes	NICE	26	12	1.6.28 The stop criteria should be altered to either a 3% weight loss **OR** a reduction in HbA1c of 1% at 6 months. Studies have shown that only 24% of patients are likely to achieve this current criteria but 46% will be able to achieve one of these targets. If the GLP-1 is stopped , the patient is likely to undergo reversal of improvements . ***Hall GC. Et.al. Diabet Med.2013Jun;30(6):681-6***	Thank you for your feedback. The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH

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						GLP-1 analogues have different efficacy . Following the guidelines suggesting the lowest acquisition cost GLP-1 analogue to be used , this will mean that only the short duration therapies will be prescribed . Before stopping the GLP-1 analogue as a class ,there should be a comment to suggest a trial of a longer acting analogue.	insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal (and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is. Recommendations in this section that cover

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							glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the GDG was not convinced of the purported material differences between the various preparations. Recommendation 1.6.17 (NICE short version) states that "if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost".
38	SH	Aneurin Bevan University Health Board	NICE	26	22	The current strategy is to encourage the management of patients with diabetes within Primary Care and for Secondary care to deal with acute and the more complicated patients. If GLP-1 analogues can only be used in combination with insulin under 'specialist supervision', patients can never be discharged to Primary Care clinics. This combination of therapy should be initiated by a clinician with training and experience; there should be criteria within the guidance to allow for discharge from a specialist clinic. The guidance also suggests a GP with specialist interest would be suitable to manage this combination. We would suggest that this term is changed to a locally recognised clinician with specialist interest. This would then allow Community Nurse consultants, independent Prescribing Diabetes Nurses and GPs with specialist skills to be included in the management of these patients.	Thank you for your feedback. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the guideline development group (GDG) agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary team.

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51	SH	Primary Care Diabetes Society	NICE	26	22	The current practice is to try and encourage management of patients with diabetes to be carried out in Primary Care and for Secondary care to deal with acute and the more complicated cases. If GLP-1 analogues can only be used with insulin under specialist supervision, patients can never be discharged back to their Primary Care clinics. Although current knowledge would suggest that this combination should be initiated by a clinician with experience, once stable, there should be criteria within the guidance to allow discharge from a specialist clinic. The guidance also suggests a GP with specialist interest would be suitable to manage this combination. We would suggest that this term is changed to a locally recognised clinician with specialist interest. This would then allow Community Nurse consultants, independent Prescribing Community Diabetes Nurses and GPs with specialist skills to be included in the management of these patients.	Thank you for your feedback. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the guideline development group (GDG) agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary team.
246	SH	South East Strategic Clinical Network	NICE	26	22	The message regarding "Specialist care " is potentially confusing and inconsistent with NHS England's National Diabetes Integrated care model. The statement suggests that GP with a special interest and accredited Consultant Diabetologists are equal and interchangeable providers of care. They are not. There is also no mention of Diabetes Specialist nurses / Nurse	Thank you for your feedback. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the guideline development group (GDG) agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support.

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						Consultants in Diabetes. In addition it is our understanding that there is no Nationally accepted criteria for the training, accreditation and ongoing competence of GPs with a special interest in diabetes. Therefore in a nationally important document such as this with potential for significant influence on service changes and commissioning it is crucial that the definition of Specialist care is clear and accurate. We believe Specialist care to indicate Diabetes Care provided by a Consultant Led Multidisciplinary Diabetes Team. Please consider the National Diabetes Integrated care service specification and align definitions between the two documents – https://www.diabetes.org.uk/Documents/Professionals/Service%20Improvement/FINAL%20Diabetes%20Sample%20Specification%20V19%2029%20July.pdf	Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary team.
275	SH	Training, Research and Education for Nurses in Diabetes	NICE	26	22	1.6.30 The current practice is to try and encourage management of patients with diabetes to be carried out in Primary Care and for Secondary care to deal with acute and the more complicated cases. If GLP-1 analogues can only be used with insulin under specialist supervision , patients can never be discharged back to their Primary Care clinics. Although current knowledge would suggest that this combination should be initiated by a clinician with experience , once stable , there should be	Thank you for your feedback. Because of the lack of evidence and that GLP-1 mimetics in combination with insulin are normally prescribed in complex cases, the guideline development group (GDG) agreed that individuals should only be offered this treatment combination with specialist care advice and ongoing support. Specialist care refers to care provided by a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care.

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						criteria within the guidance to allow discharge from a specialist clinic. The guidance also suggests a GP with specialist interest would be suitable to manage this combination . We would suggest that this term is changed to a locally recognised clinician with specialist interest. This would then allow Community Nurse consultants , independent Prescribing Community Diabetes Nurses and GPs with specialist skills to be included in the management of these patients.	The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary team.
154	SH	London Diabetes Strategic Clinical Network & Health Innovation Network (joint response)	NICE	26	General	1.6.28 **Continuing with GLP-1 memetic therapy** We are concerned that the current recommendation to only continue GLP-1 memetic therapy if the person with Type 2 diabetes has had both a reduction in HbA1c of at least 11mmol/mol and a weight loss of at least 3% in 6 months seems to disregard the important benefits of achieving either of these targets on its own. Given that GLP-1 is only considered for those who meet a strict criteria, achieving either the HbA1c reduction or the stipulated weight loss should be sufficient motivation to continue on the medication beyond 6months. We suggest rewording this section to read: *Only continue GLP-1 mimetic therapy if the person with Type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c **and/or** a weight loss of*	Thank you for your feedback. This guideline updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248 (stated in the 'Update information' section, page 8 of NICE short version). The guideline development group (GDG) noted that while triple non-insulin based drug combinations including GLP-1 mimetics (GLP-1s) had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1 triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. GLP-1 triple combinations were also shown to be not cost effective in the health economic modelling as their higher (and more certain) incremental lifetime treatment costs did not justify the marginal

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						at least 3% of initial body weight in 6 months).	(and uncertain) lifetime quality-adjusted life year (QALY) gains. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this option should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, no clinical evidence was found to suggest the starting and stopping rules should be changed, therefore the GDG agreed that, given the unclear clinical evidence and lack of cost effectiveness, the starting and stopping rules from CG87 should be retained as is.
39	SH	Aneurin Bevan University Health Board	NICE	27	2	Patient education should also emphasise safety in injection technique, management of needles and the storage of insulin. Measurers to avoid Lipohypertrophy and examination on every review of injection sites.	Thank you for your feedback. Injection technique has been added to the recommendation.
52	SH	Primary Care Diabetes	NICE	27	2	Patient education should also include safe injection technique, the safe management of	Thank you for your feedback. Injection technique has been added to the

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		Society				needles and the storage of insulin.	recommendation.
276	SH	Training, Research and Education for Nurses in Diabetes	NICE	27	2	1.6.31 Patient education should also include mode of action and benefits of prescribed medication, safe injection technique, the safe management of sharps disposal and the storage of insulin.	Thank you for your feedback. Injection technique has been added to the recommendation.
207	SH	North West Commissioning Support Unit	NICE	27	22	Clarify NPH abbreviation. No explanation in guidance that 'NPH' is Neutral Protamine Hagedorn. The guidance refers to specific named long-acting insulins and recommends 'short-acting insulins' where appropriate. The use of the term 'intermediate-acting' and NPH would seem more consistent in the guidance.	Thank you for your feedback. NPH has been added to the abbreviations.
208	SH	North West Commissioning Support Unit	NICE	27	23	We feel that the recommendation of insulin detemir or insulin glargine is not specific enough. There is a risk of greater preference for detemir insulin since it is named first in the sentence. Did this recommendation take into account of the available biosimilar insulin glargine?	Thank you for your feedback. Insulin detemir and insulin glargine are equal options. A footnote on the use of biosimilars has been added to insulin glargine which states "The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication."
227	SH	Sanofi	NICE	28	3 -5	The rationale for recommending premixed insulin in patients with an HbA_{1c} above 75mmol/mol (9%) is unclear. Premixed insulins have been shown to be associated with higher rates of hypoglycaemia and weight gain compared to basal insulins, and require patients to take their insulin at specific	Thank you for your feedback. NPH insulin once or twice daily is helpful for people with a degree of residual endogenous insulin production. When insulin production is much reduced, this will be reflected in a relatively high HbA1c initially, and a

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						times in relation to meals, which may impact on lifestyle and compliance. If clinicians do not fully understand NICE's rationale for recommending the use of an alternative treatment such as premixed insulin in patients with high HbA_{1c}, this may lead to negative consequences for the patient. We therefore urge NICE to consider adding the rationale for using an alternative treatment at high HbA_{1c} levels into the guideline text. Our understanding of the rationale for this recommendation is that in patients with a high HbA_{1c} (e.g. above 75 mmol/mol (9%)) it is likely that both high fasting and high postprandial glucose is contributing to overall hyperglycaemia. Therefore it may be appropriate to initiate a treatment which targets both fasting and postprandial blood glucose in order to efficiently reduce HbA_{1c}. If this assumption is true, then we believe it would be beneficial to shift the emphasis onto the need to target both fasting and postprandial glucose, rather than to use a specific insulin regimen, which represents only one of the options available. The guidance might for completeness also mention that the use of premix has a significant impact on the risk of hypoglycaemia which should be recognised, and discussed with the patient, in forming the therapeutic decision.	disappointing response to NPH insulin alone. Such individuals also need some additional short-acting insulin. This can be given as separate injections but at the same time as NPH insulin. Or the two insulins can be used combined in a pre-mixed formulation.

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						We therefore suggest the following wording might be used: 'If HbA_{1c} is 75 mmol/mol (9.0%) or higher, consider using injectable regimens which target both fasting and postprandial glucose.'	
92	SH	AstraZeneca	NICE	29	10	*NICE: page 29 lines 10-14* *NICE: page 23 Algorithm table: insulin based treatment* *Full: General* **<u>Absence of advice on the use of add-on to insulin therapies</u>** AstraZeneca is concerned that NICE does not give clear consideration to the use of oral treatments as add-on to insulin. Such use of oral treatments is dealt with briefly in the chapter on insulin-based treatments *[page 29 line 10-14 short guideline*] but is not mentioned in the main algorithm table. This represents a significant omission. The combination of oral agents such as metformin, SGLT2-is and DPP4-is with insulin has the potential to mitigate weight gain, limit risk of hypoglycaemia and potentially improve concordance with therapy (1,2,3,4,5). As an example, addition of an SGLT2-i to an insulin regimen has been reported to improve glycaemic	Thank you for your feedback. The recommendations are based on the clinical effectiveness review and health economic modelling analysis of available evidence with a cut off search date of June 2014, and not only the available licensed combinations. Where evidence was available, recommendations on specific treatment combinations have been made.

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						control while reducing body weight (2): such benefits may be maintained over years (6). **Recommendation** Introduce a new box providing guidance on the use of oral agents (including metformin, SGLT2-is and DPP4-is) as add-on to insulin insulin treatment. 1. Bergenstal RJM, Whipple D, Noller D, Boyce K, Roth L, Upham P, Fish L, Debold R: Advantages of adding metformin to multiple dose insulin therapy in type 2 diabetes (Abstract). Diabetes 47:A89, 1998 2. Wilding JPH. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial Ann Intern Med. 2012 Mar 20;156(6):405-15. 3. Yki-Järvinen H. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 327:1426–1433, 1992 4. Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, van der Burg BB, Konker AJM, Stehouwer CDA: Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 25:2133–2140, 2002 5. Frandsen CS.Efficacy and safety of dipeptidyl peptidase-4 inhibitors as an add-on to insulin treatment in patients with Type 2 diabetes: a review.	

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						Diabet Med. 2014 Nov;31(11):1293-300 6. Wilding JPH. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years Diabetes, Obesity and Metabolism 16: 124–136, 2014.	
192	SH	Newcastle University	NICE	29	10 -14	Important safety issues which appear very late in guideline development are always difficult to handle, particularly when inconclusive. Previous NICE T2DM guidelines did however deal well and with a good deal of foresight with the rosiglitazone issue. The regulatory warnings over ketoacidosis in people using SGLT2b's are now public domain, and while probably the issue is one of bad clinical practice, they cannot be ignored here given this text on SGLT2b's and insulin is included . A statement such as 'Regulators have very recently expressed concern that unrecognized ketoacidosis may occur in people using SGLT2-blockers, perhaps due to amelioration of signals of hyperglycaemia (see 1.6.15); the issue should be addressed prospectively with anyone using SGLT2-blockers and insulin.' might be added.	Thank you for your feedback. With regard to the recent Medicines and Healthcare products Regulatory Agency (MHRA)'s safety alert on SGLT2s, given that the current guideline is cross-referring to NICE technology appraisals, it is anticipated that this information would be included in the technology appraisal guidance. NICE is also exploring different ways of presenting this information.
116	SH	Diabetes Strategic Clinical Network Yorkshire and Humber	NICE	29	20	GASTROPARESIS is a relatively rare and - even specialists find it difficult to manage.A statement about referring to specialist services should be at the beginning of this section-not as an afterthought at the end.	Thank you for your feedback. It was not within the scope of the guideline at this update to consider gastroparesis.
63	SH	British Medical	NICE	30	General	1.7.3 We have concerns that the use of antibiotics for	Thank you for your feedback. It was not within the scope of the guideline at this

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		Association				non-infective indications may lead to an increase in resistance and is contra to other aspects of health policy.	update to consider gastroparesis.
179	SH	National Diabetes Nurse Consultant Group	NICE	31	24	There is link to the renal guideline which in turn send the reader back to the 2008 Type 2 and 2004 Type 1 guidance- so offers no other guidance . Please can the guideline committee state whether there is any other different information re medicines management in type 2 diabetes medications such as risk of hypoglycaemia as kidney function deteriorates	Thank you for your feedback. The recommendations in NICE Chronic kidney disease guideline CG182 do not refer to type 1 or type 2 diabetes guidelines. Recommendation 1.6.17 (NICE short version) emphasises the need to consider comorbidities and polypharmacy when selecting drug treatments. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy • the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the

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							lowest acquisition cost). [new 2015]
280	SH	Training, Research and Education for Nurses in Diabetes	NICE	31	24	There is link to the renal guideline which in turn send the reader back to the 2008 Type 2 and 2004 Type 1 guidance- so offers no other guidance. Please can the guideline committee state whether there is any other different information re medicines management in type 2 diabetes medications such as risk of hypoglycaemia as kidney function deteriorates	Thank you for your feedback. The recommendations in NICE Chronic kidney disease guideline CG182 do not refer to type 1 or type 2 diabetes guidelines. Recommendation 1.6.17 (NICE short version) emphasises the need to consider comorbidities and polypharmacy when selecting drug treatments. 1.6.17 For adults with type 2 diabetes, discuss the benefits and risks of drug treatment, and the options available. Base the choice of drug treatment(s) on: • the effectiveness of the drug treatment(s) in terms of metabolic response • safety (see Medicines and Healthcare products Regulatory Agency [MHRA] guidance) and tolerability of the drug treatment(s) • the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy • the person's individual preferences and needs • the licensed indications or combinations available • cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [new 2015]
28	SH	Successful	NICE	36	General	2.5	Thank you for your feedback.

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		Diabetes				Very much welcome this recommendation for more research	

Registered stakeholders: http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0612/documents