SIGN Diabetes Consultation

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Please note that section numbers refer to the consultation version of the draft guideline unless otherwise noted.

Invited reviewers			Type of response and declared interests
SB	Professor Stephen Bain	Professor of Medicine (Diabetes), ABMU Health Board & Swansea University	Individual response. Remuneration from employment - I have been a senior clinical academic since 1993 and since that time report having received honoraria, teaching and research sponsorship/grants from the following: Abbott, Astra-Zeneka, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-aventis, Schering-Plough, Servier & Takeda. I have also received funding for the development of educational programmes from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med & Medscape. Remuneration from self employment - I am a partner in Glycosmedia which carries sponsorship declared on its website.
AB	Professor Anthony Barnett	Emeritus Professor of Medicine/Consultant Physician, Birmingham	Individual response. Remuneration from consultancy – I have received honoraria for lectures and advisory work from Janssen, MSD, Novartis, Astra-Zeneca, Boehringer-Ingelheim, Eli Lilly, Sanofi-aventis, NovoNordisk.
GB	Mrs Gillian Booth	Specialist Pharmacist, Diabetes and Endocrinology, Forth Valley Royal Hospital	Individual response.

ME	Dr Marc Evans	Consultant Diabetologist, University Hospital, Llandough, Cardiff.	Individual response. Remuneration from consultancy or fee paid work – I have received research awards and speaker fees from a variety of pharmaceutical companies including Novo Nordisk, Sanofi, Eli Lilly, MSD, Novartis, Boehringer Ingelheim, Merck and Jansen.
MF	Professor Miles Fisher	Consultant Physician, Glasgow Royal Infirmary, Glasgow	Individual response. Remuneration from consultancy – Consultation and/or lecture fees: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, MSD, Novartis, Novo Nordisk, Sanofi, Servier, Takeda.
AG	Dr Andrew Gallagher	Consultant Physician & Endocrinologist, Honorary Clinical Associate Professor, Glasgow	Individual response.
NG	Dr Nazim Ghouri	Consultant Diabetologist and Honorary Senior Clinical Lecturer, Queen Elizabeth University Hospital/ University of Glasgow	Individual response. Remuneration from employment - Have given 3 talks on management of patients with T2DM on behalf of Astra Zeneca.
FG	Dr Fraser Gibb	Consultant Endocrinologist, Royal Infirmary of Edinburgh	Individual response. Remuneration from consultancy - Attendance at EASD 2014 and ADA 2014 sponsored by Novo Nordisk
SJ	Dr Scott Jamieson	General Practitioner, Kirriemuir Medical Practice, Kirriemuir. (GP representative for SIGN Council).	Individual response.
BK	Dr Brian Kennon	Consultant Physician, Queen Elizabeth University Hospital, Glasgow	Individual response. Remuneration from employment - Speaker fees from NovoNordisk and Lilly for presentation

			about diabetes. Not specifically for any pharmaceutical product so unclear if this needs t be specifically declared however I have included it for completeness.
SMac	Mrs Susan MacFarlane	Pharmacist Prescriber, Craigshill Health Centre, Livingston	Individual response. Remuneration from employment – Specialist interest in Diabetes (Type 2). Employee of Boots Pharmacy and Lothian Health Board.
SM	Professor Sandra MacRury	Consultant Diabetologist, Raigmore Hospital, Inverness	Individual response.
JM	Dr Joan McDowell	Senior Lecturer, University of Glasgow, Glasgow.	Individual response. Remuneration from consultancy – I am a member of the UK NovoNordisk Research Committee.
JMc	Professor John McKnight	Consultant, NHS Lothian, Edinburgh	Individual response. Remuneration of paid office - I work in the R and D department of NHS Lothian and we do carry out some commercial studies of new drugs in diabetes. These include the newer therapies presented in this latest guideline, and these do make money for and R and D account that I manage. I received support to attend EASD from Novo last year but no other support or finances. Non-personal support from commercial healthcare companies – Same as above.

Open consultation			Type of response and declared interests
ABI/EL		Alliance Boehringer Ingelheim UK – Eli Lilly UK	Group response. Nature of organisation – Pharmaceutical manufacturer. How might statements & recommendations impact on your organisation? – Our organisation would be weakened following a recommendation in favour of/against these intervention as it would decrease management options for patients in Scotland. Our organisation wants to ensure that the data is presented in an accurate, fair, balanced and consistent way in the best interest of patients with unmet medical needs.
ABPI		ABPI Scotland	Group response. Nature of your group - The Association of the British Pharmaceutical Industry Scotland are the representative trade body of the research based pharmaceutical industry in Scotland. How might statements & recommendations impact on your organisation? - As the representative body of the pharmaceutical industry in Scotland and an important partner in the care of Scottish patients, it is important that the view of ABPI Scotland is considered as part of this consultation.
AZ		Astra Zeneca PLC	Group response. Nature of your group – Pharmaceutical

			Manufacturer. How might statements & recommendations impact on your organisation? – AstraZeneca agrees that the SIGN guideline should be aimed at giving type 2 diabetes patients in Scotland timely treatment with the right medicines to minimise the risk of complications arising from the condition. Given all of AstraZeneca diabetes medicines belong to classes of medicines viewed as standard of care in Scotland, which are already incorporated into the SIGN 116 guideline, we do not believe the update will significantly increase or decrease company performance assuming our additional comments are sufficiently incorporated.
MC	Mr Martin Charlton	Farmer, Bunanta Taynuilt, Oban	Individual response.
DS		Diabetes Scotland	Group response. Nature of your group – Charity representing the views of people living with diabetes. How might statements & recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
AGo	Dr Ann Gold	Consultant Diabetologist, Aberdeen Royal Infirmary, Aberdeen,	Individual response. Remuneration from consultancy – I have participated in educational meetings which have been funded by a variety of pharmaceutical companies and have received and honorarium for these

			meetings. Non-financial interests – I have been a member of the DVLA Diabetes and Driving Advisory Panel for the last 15 years.
RG	Ms Rosanne Goodwins		Individual response.
EL		Eli Lilly	Group response. Nature of your group – Pharmaceutical manufacturer. How might statements & recommendations impact on your organisation? - Lilly remains committed to the management of glycaemic control in people with type 2 diabetes across the entire treatment algorithm. Therefore, we support the development of guidelines that enable clinicians in primary and secondary care to make informed decisions about treatment options for their patients in line with Scottish policy. To this effect, we believe it is pertinent to be able to view and comment on the revised treatment algorithm before the final guidance is published.
MSD		Merck, Sharp and Dohme	Group response. Nature of your group – Pharmaceutical manufacturer. How might statements & recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
JN		Janssen Pharmaceuticals & NAPP	Group response.

		Pharmaceuticals	Nature of your group – Pharmaceutical manufacturer. How might statements & recommendations impact on your organisation? - The draft SIGN recommendation in favour of canagliflozin (and SGLT2 inhibitors in general) would promote uptake in NHS Scotland which may increase company performance for all marketing authorization holders of SGLT2 inhibitors.
NHSLot		NHS Lothian	Group response. Nature of your group – NHS Board How might statements & recommendations impact on your organisation? – Doctors and nurses working in primary care will be disappointed if there is not more specific guidance in this document. It is felt the guidelines do not do enough to clarify when each agent should be prioritised/considered, particularly as the algorithm tying it all together is not included in this draft
NHSGGC		Community Diabetes Dietitians, NHS GG & C	Group response. Nature of your group – NHS GG & C Community Diabetes Dietitians. How might statements & recommendations impact on your organisation? – Influence local policies.
NHSsig		NHS Scotland Special Interest Group Diabetes: Pharmacy	Group response. Nature of your group – NHS group of pharmacists working in diabetes primary and secondary care. The main themes of

			the group's work include SG Effective Prescribing Programme, Transformational Change in Primary Care, Benchmarking and the Carter report. How might statements & recommendations impact on your organisation? – Recommendations in the guidance will impact on prescribing expenditure at time when this is insufficient resource to meet demand.
NovNo		Novo Nordisk Ltd	Group/Organisation response. Nature of your group – Pharmaceutical Manufacturer. How might statements & recommendations impact on your organisation? – In general, we believe that the draft recommendation, which does not recommend liraglutide for people with type 2 diabetes at high risk of cardiovascular disease and does not specifically mention insulin degludec, will limit the best treatment options for patients in Scotland. We also consider the algorithm to be of high impact in the implementation of the final guideline and hope this will be subject to a further consultation to ensure sufficient clarity and patient centricity.
NP	Professor Neil Poulter	Professor of Preventive Cardiovascular Medicine, Imperial College, London	Individual response. Remuneration from self employment - I have received honoraria for being a member of the Steering Committee of the LEADER, DEVOTE and EXSCEL trials. I have also

			received speaker honoraria for lecturing at scientific meetings in the field of glucose-lowering by Novo Nordisk, Takeda and AstraZeneca.
RCP		Royal College of Pathologists, London	Group response. Nature of your group – Professional organisation of pathology specialties in UK. How might statements & recommendations impact on your organisation? – 'Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation'.
RCPE		Royal College of Physicians, Edinburgh.	Group response. Nature of your group – Medical Royal College. How might statement & recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
RCPL		RCPL, Joint Specialist Committee for Endocrinology and Diabetes	Group/Organisation response. Nature of your group – RCPL – Charity. How might statements & recommendations impact on your organisation? – May impact on future national guidance in other parts of the UK.
Sa		Sanofi	Group/Organisation response. Nature of your group – Pharmaceutical

			Manufacturer. How might statements & recommendations impact on your organisation? – The SIGN guideline will influence HCP prescription habits, therefore having the potential to influence the volume of our manufactured goods.
Ta		Takeda UK	Group/Organisation response. Nature of your group – Pharmaceutical Manufacturer. How might statements & recommendations impact on your organisation? – The broader recommendation for the use of DPP-4 inhibitors after metformin (i.e. in dual and triple therapy or with insulin) to the previous SIGN guideline 116 may lead to increased DPP4 inhibitor prescribing, which in turn may increase our company's performance.

Section	Comments received		Development group response
General			
	RG	I am morbidly obese with diabetes Type 2 and I believe I have received less than optimal treatment from the Glasgow Weight Loss Service.	Thank you for your comments. The remit of the guideline is glucose-lowering therapies. Please refer to SIGN 116 on lifestyle modification for further information on weight management.
	AG	The style follows a well established pattern and I have no issues with it. A good and thorough job well done.	Noted. Thank you.
	AB	Looks good to me but as I have indicated I have several reservations particularly relating to some of your recommendations.	Noted. Thank you. We address these individual below.
	GB	The flow chart was not available to view which would have useful as this is used to inform local guidance and an easy to follow layout is essential. It would have been better if the new additions were highlighted more clearly and the changes made more obvious for reviewing.	Noted. Thank you. We consulted separately on the algorithm before publication. The summary of updates is included in section 1.2. We believe that all recommendations, whether original or new are equally valid and should be implemented.
	SB	The whole guideline is surprisingly old-fashioned and makes the current NICE guideline seem very modern. A major surprise given the reputation of SMC and Scotland in general.	Thank you.
	MC	12 Algorithm for glucose lowering in people with type 2 diabetes – NOT INCLUDED IN THIS VERSION. Without seeing what is proposed it is hard to comments, but an algorithm which does not even mention, arguably, the best intervention for T2D is likely to worsen outcomes for patients. In general this is a clear and well presented answer to the annex 1 questions.	Thank you. We consulted subsequently on the algorithm before publication.
	MF	It is unfortunate that the algorithm is not available at the point in time. This guideline provides updated information on each of the drugclasses that were available in 2010 plus adds information on SGLT2 inhibitors, which were not available in 2010. If we accept that metformin is the first line choice then there are multiple second and third line choices (SUs, pioglitazone, acarbose, DPP-4 inhibitors, SGLT2 inhibitors, GLP-	Thank you. We consulted subsequently on the algorithm before publication.

		1 RAs, insulin). In each section the possible benefits and side effects are described for each class/drug and it is hoped that the algorithm can provide guidance on how to choose the next drug, eg if the patient is obese and wants to avoid weight gain, wants to avoid hypoglycaemia, has existing cardiovascular disease, etc.	
	SMac	Recommendations perfect at relevant points. Particularly like checklist for provision of information and sources of other information.	Thank you.
	BK	As before an executive summary and tables with the different classes of agents would be useful. Apologies if there is plans to include this and the algorithm also covers some of these points.	Key recommendations have been included and a quick reference guide will be published. The algorithm includes summary information about all of the classes included in the guideline.
	SJ	Overall, really no other significant issues from my GP perspective other than the $HBA1_C$ target.	Thank you
	AGo	I share my comments as the retiring chair of the Driving and Diabetes Advisory Panel. Not informing health professionals about the implications for driving leaves them wide open to complaint and potentially litigation if any incidents arise as a result of a lack of information provided to the patient.	Agreed. We have added updated DVLA advice into the Provision of Information section.
	RCP	Very well written and presented, accessible and clear.	Thank you
	RCPE	There is no data on or mention of fixed dose combinations, which have the potential benefits to patients and may improve adherence as well as saving money. Language does future proof parts of the guideline but it should be generalised further as the guideline could be out of date very quickly. We look forward to seeing the algorithm that was not included in this draft.	Thank you. We did not identify specific evidence on fixed dose combinations. NICE (p80) also did not identify evidence, but made a consensus statement. We will have a comment in the Provision of Information section regarding adherence and fixed dose combinations.
	RCPL	Info on BGM with SU use.	Glucose monitoring is covered in SIGN 116, and is not included in the remit of this document, however we have added information to the Provision of Information section to clarify changes to the DVLA requirements.
	JM	It is good to see this part of SIGN 116 updated as it is an area that is evolving at quite a rapid pace of change. The	Thank you. the management of blood glucose in the dying person is outwith the remit of this guideline. We have updated

		Algorithm is essential for this. Is there a place for considering a separate section on the management of blood glucose in the dying person?	section 1.2.1 (the remit of the guideline) to clarify this exclusion.
	SM	Clear easy to follow.	Thank you
	Sa	We would like to request further information regarding section 12 (algorithm) as this is currently left blank.	Thank you. We consulted subsequently on the algorithm before publication.
	AZ	The Algorithm: AstraZeneca would welcome the opportunity to comment on the algorithm when it is made available as it is integral to the guidance.	Thank you. We consulted subsequently on the algorithm before publication.
	NovNo	We would like to suggest a short consultation on the draft algorithm prior to guideline completion, as this can potentially impact on its clarity and affect the essence of the guideline itself and consultation can be helpful to mitigate against any problems with clarity.	Thank you. We consulted subsequently on the algorithm before publication.
	ABPI	ABPI Scotland welcome the update of the glucose section of SIGN 116, and we share the same ambition to support clinicians to make good choices in order to better manage patients with diabetes in Scotland. We commend SIGN for the progress made, and the speed at which the review has occurred. It would be very helpful if the format of each section was standardised as there are inconsistency of formatting within each section and this makes interpretation and implementation less clear. The whole document would benefit from some revision to make it one cohesive document. In order to future proof SIGN guidelines, it would be helpful to include a horizon scanning section of clinical trial work. In particular on the mandatory cardiovascular trials which all diabetes companies have recently been asked to complete on their medicines. These will be published in the medium term and this would also apply across the classes for differing clinical outcomes. It is important for clinicians to be aware and up to date with these trials when considering treatment for patients with high cardiovascular risks. The Algorithm - The Algorithm is integral to the guidance and therefore should be released for	Thank you We have standardised the structure of sections as much as possible. Variation in subheadings is not accidental but reflects comparators used for different drug classes. We have added a paragraph in section 1.1.1 to explain the single addition made to section 3. This is not a step in SIGN guideline development methodology. We have, however, indicated ongoing studies where we feel these to be particularly important. Thank you. We consulted subsequently on the algorithm before publication.

		comment before publication of the guidelines. We would welcome the opportunity to comment on the algorithm, having taken account the feedback from all stakeholders, in order to ensure it is reflective of the main schedule.	
	EL	The revised treatment algorithm should be made available for consultation once drafted before publication of the final guidelines.	Thank you. We consulted subsequently on the algorithm before publication.
	NHSLot	Overall, the evidence for different treatment modalities has been updated and the section on SGLT2 inhibitors is welcomed. However, the recommendations remain rather bland and arguably fail to give enough guidance to the non-specialist. The biggest draw-back of this draft guideline is that it does not include the crucial algorithm which will give guidance on how and when the various drug classes should be preferentially used. The algorithm is likely to be the section of the guideline which is most referred to by GPs. It is to be hoped that the algorithm will differentiate between patients with established cardiovascular disease, in whom there is current evidence of cardiovascular benefit associated with the use of empagliflozin and liraglutide.	Thank you. We consulted subsequently on the algorithm before publication. The algorithm highlights the specific agents within classes (SGLT2 inhibitors and GLP-1 receptor agonists) which are associated with cardiovascular benefits.
	JN	Janssen and Napp appreciate the opportunity to consult on the draft type 2 diabetes guidelines and would like to commend the writing committee on the methodology employed that provides a transparent summary for health care professionals, patients and policy makers. Please could the algorithm be made available for consultation?	Thank you. Thank you. We consulted subsequently on the algorithm before publication.
Section 1			
1.1	AG	New medications arriving on the market and results from important clinical trials make this guideline a timely development.	Noted. Thank you
	AB	Agreed	Noted. Thank you.
	JMc	Yes needed as SIGN not up to date in this area.	Noted. Thank you.
	MF	This is a well written draft guideline. The methodology is complex and is clearly described. The key parts of the guideline which will receive the most attention in clinical practice are the key recommendations (KRs) and the algorithm.	Noted. Thank you.

	BK	Clear and appropriate.	Noted. Thank you.
	RCP	Comprehensive.	Noted. Thank you.
	ME	The need for a guideline is clearly outlined and reflected within the document. There is particular need for new guidance for treating type 2 diabetes based on the plethora of new agents and the growing data such as the cardiovascular outcome studies and novel insulin therapy studies such as SWITCH 1 and 2	Noted. Thank you. SWITCH 1 is not relevant for this guideline, and SWITCH 2 was published outwith the search period for this guideline.
	JM	Satisfactory.	Noted. Thank you.
	SM	Important as increasing number of people with type 2 diabetes and with the majority managed in a community or non specialist setting.	Noted. Thank you.
	NHSLot	It is agreed a guideline is required.	Noted. Thank you.
1.1.1	AG	As above. Since the last SIGN Diabetes guidelines there have been a number of developments.	Noted. Thank you.
	AB	Agreed	Noted. Thank you.
	BK	Again clear and appropriate.	Noted. Thank you.
	RCP	Comprehensive.	Noted. Thank you.
	ME	Some critical pieces of evidence are not included within the current evaluation, in particular the results won the SWITCH studies as well as soon to be published data such as CANVAS and the DEVOTE trial. The data derived from these studies would greatly inform the guideline development.	SWITCH 1 is not relevant for this guideline, and SWITCH 2 was published outwith the search period for this guideline. We have since considered the major new cardiovascular outcome trials (CVOTs) as they were published between the date of the SIGN searches and the cut off for publication.
	JM	Good rationale given.	Noted. Thank you
	SM	Important given the large number of relevant trials in recent years.	Thank you
	DS	We strongly believe that the guidelines should include explicit information on self-blood glucose monitoring. This would guide healthcare practitioners who prescribe medications that induce hypoglycaemia to discuss the need for self-blood glucose monitoring, hypo management, driving regulations etc.	This information is included in SIGN 116. We have added in further information to the Provision of Information section to highlight the latest DVLA requirements.
	NHSLot	Since the last guideline (SIGN 116), there has been some significant cardiovascular safety data to draw on and this is rightly introduced early on in section 1.1. However, greater emphasis should be	Thank you. We believe that the appropriate emphasis is currently given.

		given to cardiovascular data in the sections on GLP-1 analogues and SGLT2 inhibitors.	
1.2.1	AG	Achieved and done so in a concise and constructive way.	Thank you
	AB	Agreed	Thank you
	BK	Good.	Thank you
	RCP	Well reasoned.	Thank you
	ME	The guideline objectives are entirely appropriate.	Thank you
	JM	Appropriate.	Thank you
	SM	Relevant, however, would have been useful from a clinical practice stand to see evidence for use of type 2 therapies in renal impairment. Would have been useful to have seen a draft of the intended algorithm and with the inclusion of information to aid prescribing in renal impairment.	Thank you. Noted. The safety and efficacy of glucose-lowering agents vary even within classes across the spectrum of renal impairment and over time. We have since summarised information on use of the different classes in CKD stage 3A in the algorithm, and have also referred the reader to the summary of product characteristics (SPC). We consulted subsequently on the algorithm before publication.
	NHSLot	The sections on metformin, sulphonylureas and glitazones are consistent with currently accepted practice and rightly continue to favour metformin as a first line agent with sulphonylureas next in line, ahead of newer but more expensive drugs with less long term experience to back them up. Pioglitazone treatment is qualified by appropriate caveats round heart failure and bone health.	Thank you.
1.2.2	AG	Excellent and up to date. Well structured, clear and concise.	Thank you
	AB	Agreed	Thank you
	MF	For the recommendations some of these are unchanged from 2010, some of these contain a minor change, and some of these are new. It would be helpful if there was a mark beside each recommendation indicting no change, minor change, new recommendation, and for the 2010 recommendations that have been changed the original should be included in an appendix for comparison.	Thank you. This is not standard SIGN methodology. We believe that it does not make a difference to the general reader whether a recommendation was developed in 2010 or 2017 as all recommendations should be treated in the same way by healthcare professionals.
	BK	Overall I think the document is an excellent summary and analysis of the	Thank you

		latest evidence with regard the pharmacological treatment of type 2 diabetes. It is unfortunate we can't see the treatment algorithm as this will likely have the greatest impact, especially when non-specialists are using the guideline. I'd be concerned it is too generic with a lack of a clear steer as to which agents to use when. It may be the algorithm covers this which would be excellent. I would have thoughts that there is enough evidence to recommend specific GLP-1s given the varying evidence base within that class. There is no recommendation to use a GLP-1 receptor agonist with evidence of cardiovascular benefit when starting this type of drug in overweight patients with established CV disease (as was recommended for SGLT2 inhibitors). Finally, a table of the different classes of drugs comparing HbA1c reduction, side effects such as weight and hypos, CVS outcomes etc. would be useful. I'm not sure if this has been planned or not.	Thank you. We consulted subsequently on the algorithm before publication. Thank you. The algorithm will assist clinicians to choose the most appropriate agents for individual patients. A recommendation has been added to section 9.3 (updated version) to reinforce the potential for benefit in high-risk patients when using GLP-1 agonists with proven cardiovascular benefit. The algorithm will help to provide advice on the key clinical outcomes associated with the drugs.
	AGo	There are very few references to the need for blood glucose monitoring in relation to driving. On page 32 there is a minor comment but the most important issues have been omitted. As both DVLA and NICE recommend blood glucose monitoring in patients on sulphonylureas with a Group 1 licence this should be included. For those with Group 2 licences monitoring is mandatory on sulphonylureas. The information from the table Assessing Fitness to Drive would be useful to include and the reference provided should be Assessing Fitness to Drive.	Agreed. This has been added to the provision of information section and a cross reference to DVLA made. The DVLA information has been reviewed and considered for inclusion (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/596959/assessing-fitness-to-drive-a-guide-for-medical-professionals.pdf)
	RCP	Clear and well summarised.	Thank you
1.2.3	AG	Anyone managing diabetes in primary and secondary care. All staff: medical, nursing, dietetic and podiatry.	Disagree. We have already highlighted "healthcare professionals involved in the management of people with type 2 diabetes…" We have further revised the wording of this section to clarify that we are targeting prescribing.
	AB	Agreed	Thank you
	BK	I think it is appropriate for both diabetes specialists and for primary care staff. As	Thank you. We consulted subsequently on the algorithm before publication.

		detailed (1.2.2) more directive guidance may be of use for non-specialists.	
	RCP	Comprehensive.	Thank you.
	ME	HCPs involved with diabetes care.	Thank you.
	JM	Should include Diabetes Nurse Specialists as many of them are also Nurse Prescribers.	Agreed. This has been added.
	SM	Should include Diabetes Specialist Nurses and Practice Nurses.	Agreed. This has been added.
1.3	AG	Clear.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	BK	Good.	Thank you. Noted.
	RCP	Clear.	Thank you. Noted.
	JM	Appropriate.	Thank you. Noted.
1.3.1	AG	Certainly extensive questioning regarding this!	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	BK	N/A.	Thank you. Noted.
	RCP	Transparent.	Thank you. Noted.
	ME	None.	Thank you. Noted.
	JM	Satisfactory.	Thank you. Noted.
1.3.2	AG	Well covered.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	SMac	Relevant.	Thank you. Noted.
	BK	N/A.	
	RCP	This was very well and clearly written.	Thank you. Noted.
	ME	The guideline supports on label prescribing.	Thank you. Noted.
	JM	Satisfactory.	Thank you. Noted.
1.3.3	RG	I have been refused surgery time and again. First because I failed to complete the 2 year weight loss program, then because I was repeatedly told there is no mechanism for being fast-tracked despite my state of health and the benefits I would rcv from surgery and the latest is because I am too old, too fat and my diabetes was diagnosed too long ago! All of which I believe to be spurious reasons, imposed by beancounters rather than for any clinical reason.	Thank you for sharing your experiences. Bariatric surgery is not within the remit of this guideline on glucose-lowering therapies.
	SMC	As you will be aware, from 1st October 2017, NICE MTAs will no longer be assessed by Healthcare Improvement Scotland so this section should be	Thank you. SIGN has updated its standard text for inclusion in all new guidelines to reflect this.

		updated to reflect this change. The second paragraph should be amended to read "The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly-licensed medicines, ***all new formulations of existing medicines*** and new indications for established products."	Agreed. Revision has been made.
	AG	Very good as one would expect it to be.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	BK	N/A.	
	RCP	Clear.	Thank you. Noted.
	ME	Health technology assessments require both cost effectiveness along with short term budget impact evaluations. Real world data may be very useful in informing such discussions	Thank you. Noted.
Section 3			
General	JN	Please could the key recommendations be made available for consultation?	These will not be circulated, however they are drawn from the main body of the guideline which has been circulated.
3.1	RCPL	Focus on different targets with ageing, frailty, renal disease-anaemia.	Noted, this section has not been updated, however individualisation is highlighted in the algorithm.
	AG	Takes in to play all those relevant trials and scrutinizes appropriately. Exactly what one would expect of the SIGN process. No-contentious issues and data up to date.	Thank you
	AB	Agreed	Thank you
	SB	The unchanged text on targets for glycaemic control (pages 6–8) mention HbA1c only in terms of % and this may make the section difficult to understand for healthcare professionals brought up in the mmol/mol era. P10. I am surprised that the CV benefits of metformin in 342 overweight patients should be graded as '1++' evidence.	Disagree. All HbA1c targets have values in % and mmol/mol. This was retained from SIGN 116 and has not been re-appraised. The study was conducted at an earlier time when trial methods were less stringent than the current era.
	MC	HbA1c is a measure indicating average blood glucose over time. Far more important in terms of side effects of T2D is the frequency and intensity of blood glucose levels, and the insulin response to them. Why does this section refer to metformin,	Thank you. Trials assessing the efficacy of glucose-lowering agents typically utilise HbA1c as the primary outcome measure. Diet as a treatment for type 2 diabetes is covered in SIGN 116.

		it would be more appropriate to look at lifestyle specifically using a low carbohydrate moderate protein high fat diet?	
	MF	Recommendation on HbA1c target is fine.	Thank you
	BK	Unchanged.	Thank you
	SJ	I think we need to adjust the main recommendation from this section. The conclusion that 7% is a reasonable target is misleading. What we mean is that anything less than 7% is harmful. Moreover, at the expense of possible complications of therapy to get to this target, we may cause harm to gain improvement on surrogate markers with no improvement in all-cause mortality. There have been no major RCTs to identify any $HBA1_c$ target and we must be clearer on this. So where I appreciate that $HBA1_c$ has been a great tool to use as a marker of glycaemic control, I think we must be clearer in the recommendation of its limits and the problems which may result from chasing this target. *Rémy Boussageon, Denis Pouchain and Vincent Renard Br J Gen Pract 2017; 67 (655): 8587. DOI: https://doi.org/10.3399/bjgp17X689317*	Disagree. Several trials referenced (eg ACCORD, ADVANCE and VADT) provide evidence which broadly supports a target HbA1c of 7.0% (53 mmol/mol).
	RCP	Comprehensive.	Thank you
	RCPE	There is no mean duration of diabetes of diabetes for the VADT study – is this consistent?	Thank you. This has been added (mean duration 11.5 years).
	ME	Glycaemic targets are appropriately evaluated.	Thank you
	JM	I wonder if p values should be included in this section. If p values were not statistically significant, this should be stated.	Disagree. When estimates of effect of continuous variables are presented, they are accompanied by confidence intervals. These indicate not only the precision of the estimate and the range of possible results, but also determine the statistical significance at the level of confidence associated with the type of confidence interval (eg 95%). The p-value alone, contains less information and when added to the confidence interval does not express any incremental information. Therefore, p-values for effect ratios have not been added. They are retained when comparing two distributions of mean values where confidence intervals are not appropriate. This approach has recently been adopted by Healthcare Improvement Scotland

	AZ	This study involves rosiglitazone used in combination with other oral glucose lowering drugs. Rosiglitazone was withdrawn from the UK market after the European Medicines Agency determined that its use was associated with an unacceptable risk of adverse cardiovascular events (see also section 6.2). Recommendation for blood glucose control (Chapter 3): AstraZeneca suggests the addition of a threshold to indicate when treatment intensification is recommended. We suggest amending the recommendation to: A HbA1c target of 7.0% (53 mmol/mol) in people with type 2 diabetes is reasonable to reduce risk of microvascular disease. A target of 6.5% (48 mmol/mol) may be appropriate at diagnosis. Targets should be set for individuals to balance benefit with harm, in particular hypoglycaemia and weight gain. Patients whose blood glucose rises above 7.5% (58 mmol/mol), should receive treatment intensification with the aim of bringing HbA1c down to 7.0% (53 mmol/mol) (in line with NICE adult type 2 diabetes guideline). Reference: Type 2 diabetes in adults: management (published 2 December 2015), available from: https://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-1837338615493	After the withdrawal of rosiglitazone, an independent re-analysis of the data from the CV outcome trial RECORD indicated that there was no evidence of an unacceptable risk of adverse CV events. The GDG is not aware of any evidence to support a change in glucose targets or approach to intensification from that recommended in SIGN 116. There are slight differences between these approaches but they are derived from the same evidence base: in our view, allowance for individualisation provides sufficient flexibility for appropriate clinical decisions.
	NovNo	This section positively acknowledges the multi-factorial approach required for managing people with type 2 diabetes and makes it clear that a proper patient focus is necessary to agree glycaemic targets. The recommendation recognises that issues of hypoglycaemia and weight are key to an individual's quality of life and will affect therefore the glycaemic target. We agree with this statement but would like to add at this point, and will do so again in the applicable section later on, that choosing the appropriate treatments in relation to hypoglycaemia and weight, should also feature as part of relevant treatment recommendations.	Thank you. Agreed.
3.2	AG	See comments in section 3.1.	Thank you

	AB	Agreed	Thank you
	JMc	Semaglutide study not mentioned? *N Engl J Med 2016 Volume 375(19):1834-1844*	This drug has not yet received a marketing authorisation and has not been considered by SMC.
	MC	It's no wonder HbA1c reduction by drugs does not reduce mortality given the first point above.	Thank you. No action required.
	FG	Mention of the explanatory studies of ACCORD mortality – glycation gap (10.2337/dc121040) and failure to achieve HbA1c despite intensification (10.2337/dc09-1278). Rapid reduction of HbA1c not wholly tenable as explanation.	Thank you for this valuable comment. The GDG believes that the "glycation gap" is a hypothetical construct that has yet to be empirically tested, and also of more specialist interest than warranted in the guideline. However, we decided to remove the sentence in question as it was based on a speculation that has not been supported by subsequent post hoc, hypothesis-generating analyses of ACCORD.
	BK	Good summary of the evidence.	Thank you
	RCP	Comprehensive.	Thank you
	JM	Satisfactory	Thank you
3.3	AG	See comments in section 3.1.	Thank you
	AB	Agreed	Thank you
	MC	Same as 3.2	Thank you. No action required.
	BK	Again, good summary of the evidence.	Thank you
	RCP	Comprehensive.	Thank you
	JM	Satisfactory	Thank you
3.4	AG	See comments in section 3.1.	Thank you
	AB	Agreed	Thank you
	BK	Good.	Thank you
	RCP	Comprehensive.	Thank you
	JM	Satisfactory	Thank you
3.5	AG	See comments in section 3.1.	Thank you
	AB	Worth noting that whilst "tight" glycaemic control is associated with increased risk of hypoglycaemia, all of the studies to support this included the use of insulin secretagogues and/or insulin to achieve this. By tightening control with drugs which do not significantly increase hypoglycaemia risk, the benefits are more likely to be seen without the unfortunate/ dangerous side-effect of hypoglycaemia. In your recommendations I believe these facts need to be taken into account and certainly I see no reason why target cannot be a value below 7% if drugs	Thank you. This is an interesting theory but according to SIGN evidence-based methodology the present recommendation will stand until outcome-based trials using agents other than insulin secretagogues and insulin show benefits of targeting HbA1c <7.0% versus 7.0%.

		without this problem are being used.	
	MC	Treatment to glycaemic targets using a low carbohydrate moderate protein high fat diet, does not result in an increased incidence of hypoglycaemia. It is not the treatment to target that is the problem it is the method of treatment.	Thank you. The ketogenic diet for management of type 2 diabetes is outwith the remit for this guideline.
	BK	Appropriate.	Thank you
	AGo	The driving advice mentioned above should be mentioned in this section as well as the need for monitoring.	Thank you. These have been included in the Provision of Information section.
	RCP	Comprehensive.	Thank you
	RCPE	This section only discusses problems with major hypoglycaemia for T2DM – mild/moderate hypoglycaemia also has significant QOL issues for type 2 patients.	We acknowledge that all forms of hypoglycaemia impact quality of life, but have chosen to provide the frequency of the most serious episodes across intensive and standard glucose-lowering groups. The rates of less severe hypoglycaemia are higher, though there is inconsistency in methods used to measure and report these across studies.
	ME	The implications of hypoglycaemia are evaluated satisfactorily, although data from the SWITCH 1 and 2 trials would further inform the relative hypoglycaemia profiles of analogue basal insulins, while cost effectiveness data derived from these studies (currently in abstract form) would be informative.	See above
	JM	Satisfactory	Thank you
	JN	"Targets should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain." Janssen & Napp request that clarification be included in this section that newer agents, such as SGLT2 inhibitors, are associated with weight loss and a lower risk of hypoglycaemia unlike more traditional agents References: *Canagliflozin SmPC:* https://www.medicines.org.uk/emc/medicine/28400 (last accessed 22/05/2017) *Empagliflozin SmPC:* https://www.medicines.org.uk/emc/medicine/28973 (last accessed 22/05/2017) *Dapagliflozin SmPC:* https://www.medicines.org.uk/emc/medicine/27188 (last accessed 22/05/2017) *CVDREAL:* http://circ.ahajournals.org/content/early/2017/	The effects of several classes of drugs on weight and risk of hypoglycaemia are included in sections 4-10.

		05/16/CIRCULATIONAHA.117.029190 (last accessed 22/05/2017)	
3.6	AG	See comments in section 3.1.	Thank you
	AB	Ditto for weight gain.	See above
	FG	RE: R - Higher target in elderly and frail?	As this section of the guideline was not included in the questions for update, no new evidence to influence changes to targets has been reviewed.
	JMc	How clinically important is weight gain or loss of a few Kg? There is much emphasis of this as an outcome in reading this document. What is the clinical relevance? I believe this comes from companies marketing their drugs. What is the relevance of a 2 Kg weight change in someone who weighs 90 to 130 Kg? Not a lot I would argue, yet the guideline discusses the evidence for this at length. We should be emphasising diabetes medical outcomes not cosmetic effects….	The GDG appreciates the reviewer's point that in those who are very overweight a small weight gain may seem trivial. However, it was decided to retain the table from SIGN 116 as it also illustrates the relative weight gain on intensive as opposed to conventional treatment. The patient representatives noted that weight was an important patient-centred outcome.
	MC	Treatment to glycaemic targets using a low carbohydrate moderate protein high fat diet, does not result in weight gain, it results in weight loss. It is not the treatment to target that is the problem it is the method of treatment.	Thank you. The ketogenic diet for management of type 2 diabetes is outwith the remit for this guideline.
	SMac	Interesting results from trials not what would have been expected?	Thank you
	BK	Again a good and comprehensive review.	Thank you
	RCP	Comprehensive.	Thank you
	ME	Weight gain is appropriately evaluated	Thank you
	JM	Satisfactory	Thank you
	AZ	Studies supporting the data in table 1 are mainly based on older drugs such as metformin, sulphonylureas and insulin as opposed to newer drugs such as GLP-1 inhibitors, DPP4 inhibitors and SGLT2-inhibitors (one of those included the ACCORD study, which was the only study to include DPP4 inhibitors and a GLP-1 receptor agonist, exenatide). Results on weight gain with intensive therapy are likely reflect the predominant use of older drug classes, which are well established to be anabolic, i.e. associated with weight gain.	Thank you. This table is retained from SIGN 116 and we agree that it does reflect the range of therapies available at the time of the publication of the included trials (1998–2009). As intensive therapy may include insulin at any stage, we anticipate that weight gain would be associated with more intensive HbA1c control and the relative effects between standard and intensive therapy maintained, even if the absolute weight change values differ.
	NHSsig	Under the recommendation suggest targets are set 'with' individuals.	Agreed – this has been revised.

Section 4			
General	AB	Agreed	Thank you. Noted.
	MF	Rec for metformin is fine.	Thank you. Noted.
	FG	Any comment on when this should be started – immediately at diagnosis (Diabetes Care. 2010;33:501506)? Any comment on what renal thresholds? Lack of effect of weight on response – metformin works just as well in non-obese *https://doi.org/10.1371/journal.pone.0057222,* and others.	Thank you for your comment. This decision will remain at the discretion of the treating physician. We have not included timing of initiation of therapy as a key question and so are unable to include this information (and note that it is from an observational study). Although this was not one of the key questions addressed in our literature search we agree that including advice on renal thresholds would be very useful for the reader and this has been highlighted in the algorithm. We agree that metformin is also effective for glucose lowering in non-obese patients, however the RCT evidence for cardiovascular benefit comes from an obese sub-population. For this reason we feel that the original recommendation from SIGN 116 is still valid, however the wording of the recommendations for first line drug therapies have been revised to remove reference to weight.
	JM	Satisfactory	Thank you. Noted.
	NHSLot	The sections on metformin, sulphonylureas and glitazones are consistent with currently accepted practice and rightly continue to favour metformin as a first line agent with sulphonylureas next in line, ahead of newer but more expensive drugs with less long term experience to back them up.	Thank you. Noted.
4.1.1	AG	The data provided and conclusions drawn are sound and the positioning of metformin where it should be.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	RCP	Comprehensive.	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
4.1.2	AG	No issues of contention here.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	RCP	Comprehensive.	Thank you. Noted.
	RCPE	We are not sure why canagliflozin, dulaglutide and DPP-4i data are included when none of these drugs are being	Thank you for your comment. These data were included in the update because the literature search identified new studies of

		promoted as monotherapy. To be consistent, similar data for insulin, meglitinides and alpha-glucosidase inhibitors should be included. This is the only mention of meglitinides in the guideline.	sufficient size and quality comparing metformin with other agents. Noted.
	JM	Satisfactory	Thank you. Noted.
	AZ	We are unsure why only canagliflozin's trial has been mentioned in this section when similar published clinical trial exists for dapagliflozin and empagliflozin as well. For completeness/balance we propose studies for dapagliflozin and empagliflozin are also referred to. For dapagliflozin please refer to: Two randomised, double-blind, three-arm 24-week trials in treatment-naive patients to compare dapagliflozin plus metformin, dapagliflozin alone and metformin alone. In both trial studies (dapagliflozin 5mg/10mg), combination therapy led to significantly greater reductions in HbA1c compared with either monotherapy: -2.05 for dapagliflozin + metformin, -1.19 for dapagliflozin, and -1.35 for metformin ($p<0.0001$) (Study 1); -1.98 for dapagliflozin + metformin, -1.45 for dapagliflozin and -1.44 for metformin ($p<0.0001$) (Study 2). Reference: *Henry et al Int J Clin Pract 2012 Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial.*	Thank you for your comment. While we appreciate that this study provides useful data, one exclusion criterion states that only trials with 200 or more participants per group will be accepted as evidence (see section 14.1). Although not directly referred to in the guideline text these studies were included in the AHRQ review.
4.2	AG	No issues of contention here.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	RCP	Comprehensive.	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
	AZ	We are again unsure why only canagliflozin's trial has been mentioned in this section when dapagliflozin and empagliflozin have similar trials. For completeness/balance we propose studies for dapagliflozin and empagliflozin are also referred to. For dapagliflozin please refer to: Two randomised, double-blind, three-arm 24-week trials in treatment-naive patients to compare dapagliflozin plus metformin,	Thank you for your comment. While we appreciate that this study provides useful data, one exclusion criterion states that only trials with 200 or more participants per group will be accepted as evidence (see section 14.1). Although not directly referred to in the guideline text these studies were included in the AHRQ review.

		dapagliflozin alone and metformin alone. In both trial studies dapagliflozin + metformin combination therapy was more effective than metformin for weight reduction ($p < 0.0001$). Body weight reductions respectively in Study 1 (dapagliflozin 5mg) for dapagliflozin+metformin, dapagliflozin and for metformin at week 24 were respectively (-2.66 kg, -2.61 kg and -1.29) and in Study 2 (dapagliflozin 10mg) for dapagliflozin+metformin, dapagliflozin and for metformin at week 24 were respectively (-3.33 kg, -2.73 kg and -1.36 kg). Reference: *Henry et al Int J Clin Pract 2012 Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial.*	
4.3	AG	Up to date taking on board the latest evidence.	Thank you. Noted.
	AB	Agreed.	Thank you. Noted.
	SB	P10. I am surprised that the CV benefits of metformin in 342 overweight patients should be graded as '1++' evidence.	Thank you for your comment. While we agree that there has been much debate on the validity and design of the study, SIGN 116 graded the evidence as 1++. In this update we have not identified any new CV trials for metformin and the grading of evidence has therefore not been altered.
	SMac	Agreed.	Thank you. Noted.
	RCP	Comprehensive.	Thank you. Noted.
	RCPE	There is no discussion about renal dysfunction and what level of eGFR Metformin needs reduced / withdrawn. There is also no mention of starting Metformin at a low dose and increasing slowly - this is important as these guidelines will be read by non-diabetologists.	Thank you for your comment. Questions on continuing metformin in patients with CKD arise regularly in clinical practice. Given the range of advice for the different agents available, the SIGN algorithm directs readers to the information available at BNF and SMC websites. Information about titration of treatment is included in the Provision of Information section.
	JM	Satisfactory	Thank you. Noted.
	NHSsig	Consider addition of gradual increase in dosing to offset GI side effects under recommendation.	Information about titration of treatment is included in the Provision of Information section.

Section 5			
General	RCPL	See prior.	The combination of SU and insulin is not specifically recommended in the updated guideline. Glucose monitoring is covered in SIGN 116, and is not included in the remit of this document. However, we have added information to the Provision of Information section to clarify changes to the DVLA requirements.
	AB	See my comments below. I have significant concerns re hypoglycaemia with these agents I think you underestimate this risk. Your recommendations need much more caution ie "Sulphonylureas "can" not "should" be considered as first line oral agents...".You need to expand your cautions on hypoglycaemia below and indicate that for first, second and third line use there are equally good alternatives without such a risk of hypoglycaemia (and indeed weight gain). Indeed, in the elderly and those with renal impairment the evidence is that these drugs are potentially dangerous.	The wording of the recommendation is consistent with a SIGN conditional recommendation. The algorithm demonstrates the factors which will help prescribers to choose the most appropriate treatments. For example, while SUs have an increased risk of hypoglycaemia, they also have higher glucose-lowering efficacy than some alternative agents, particularly when used early in the natural history of diabetes. Section 12 on Provision of Information contains further information on people who might have significant consequences from hypoglycaemia, eg those driving, or operating machinery.
	MF	Recommendations for SUs are fine.	Thank you. Noted.
	AGo	Need to add information about monitoring when driving with Group 1 and Group 2 licences – see comments above (3.5).	Agreed. This information has been added to the Provision of Information section and cross referred from within this section.
	RCPE	The American Diabetes Association guidelines mention low durability SUs (see UK Prospective Diabetes Study). There is no mention of this in these guidelines. There is no mention of renal dysfunction and withdrawing therapy. Clinically we still see patients on SUs at very low eGFRs. GPs tend to follow eGFR guidelines for gliptins and SGLT2i and forget SUs.	Thank you for your comment. The key questions did not investigate the durability of glycaemic response across the glucose-lowering drugs, however we are aware that sulphonylureas have higher durability than some classes (DPP-4 inhibitors) but lower durability than others (TZDs). See www.ncbi.nlm.nih.gov/pubmed/17145742 and www.ncbi.nlm.nih.gov/pubmed/26982210. We agree that sulphonylureas as per their license should be used with caution in mild/moderate renal impairment and avoided in severe renal impairment. This has been highlighted in section 5.2
	JM	Satisfactory	Thank you. Noted.
	MSD	MSD ask that additional prescribing information be provided for at risk groups	Thank you. Further information about hypoglycaemia risk has been added to

		when considering the use of sulfonylureas (SUs), i.e. patients with renal impairment, and those who are at increased risk of hypoglycaemia. NICE had previously acknowledged the risks associated with sulfonylureas by removing their automatic use at first intensification; as such these risks should be highlighted. MSD request that the guideline clearly defines patient populations that are not suitable for sulfonylureas at each stage of treatment intensification. For example, in T2DM patients, there are restrictions for those who drive frequently or for an occupation (see The use of Sulfonylureas when driving for DVLA warnings). The SPC lists the following contraindications: •diabetic precoma and coma •diabetic ketoacidosis •patients with severe renal insufficiency •patients with severe hepatic insufficiency •patients treated with miconazole • women who are lactating The use of Sulfonylureas when driving MSD ask that the GDG carefully consider and amend the clinical guideline to reflect the DVLA guidance document (March 2017). This states that drivers with T2DM who manage their condition with either sulfonylurea or glinides must comply with the following statements: Group 1 drivers (car, motorcycle): •Must not have had more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months •Drivers must be under regular medical review •Testing is dependent on clinical factors and driving frequency. Group 2 vocational drivers (bus, lorries) •No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12 months •Has full awareness of hypoglycaemia •Regularly monitors blood glucose at least twice daily and at times relevant to driving •Must demonstrate an understanding of the risks of hypoglycaemia •There are no other debarring complications of diabetes such as a visual field defect.	the Provision of Information section. This includes cross reference to the DVLA requirements for class 1 and 2 licences. A warning about the absolute contraindication for miconazole in users of gliclazide has been added to the Provision of Information section.

		Reference *Gliclazide Tablets BP 80mg, Summary of product characteristics. EMC. March 2017. http://www.medicines.org.uk/emc/medicine/27762; accessed 25 May 2017* *https://www.gov.uk/guidance/diabetes-mellitus-assessing-fitness-to-drive; accessed 25 May 2017*	
5.1	AG	Information appropriate and accurate.	Thank you. Noted.
	AB	Note NICE also recommends other alternative first line treatments to metformin including DPP-4 inhibitors and (surprisingly in my view) Pioglitazone. I emphasise the point because of serious concerns with sulphonylureas because of hypoglycaemia.	Thank you. These first-line options are discussed in sections 7.1 and 6.1.1 respectively.
	SB	P11. 5.1. My reading of the current NICE guideline (NG28) is that it recommends sulphonylureas as 'a' second or third-line treatment after metformin rather than 'the' treatment, as implied in this paragraph.	Agreed. NICE's recommendation has been clarified.
	RCP	Comprehensive.	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
	NHSsig	I find the terminology in the following statement open to misinterpretation "Results of meta-analyses of trials involving SUs in combination with metformin compared with other combinations did not favour SUs for HbA1c reduction" This was a meta-analysis of metformin-based combinations and the key point states: "Most other combination therapy comparisons had either no significant or no clinically meaningful (<0.3%) between-group differences in HbA1c between arms. Table 8 summarises the results." clarifying the statement that Met + Su was not superior nor worse than any other combination with metformin. Advise to clarify this.	Agreed. This sentence has been reworded to "Results of meta-analyses of trials for HbA1c reduction comparing combination therapy of metformin and sulphonylureas versus other metformin-containing combinations showed either no significant or no clinically meaningful (<0.3% (3.3 mmol/mol)) between-group differences in HbA1c between arms."
	EL	AWARD-2, AWARD-8: Please refer to additional information document	Evidence for combination therapy with sulphonylureas has been included from meta-analyses. AWARD-2 was identified by the SIGN searches but not included. Sufficient evidence comparing GLP-1 agonists with insulin (including dulaglutide with glargine) is already presented in section 8. AWARD-8 postdated the SIGN searches.

5.2	AG	As above.	Thank you
	AB	The UK Hypoglycaemia Study Group published a major paper in Diabetologia in 2007 which was a prospective study over 9-12 months in 6 different regions of the UK looking at hypoglycaemia in both Type 1 and 2 Diabetes. *Diabetolgia 2007;50:1140-1147* Note in Type 2 Diabetes 50% of people on insulin and 40% of people on sulphonylureas experienced hypoglycaemia in that time period. The numbers experiencing severe hypoglycaemia (needing 3rd party help) was identical in the 2 groups ie 7% of patients on insulin and 7% of patients on insulin (in the first 2 years of insulin treatment). All patients also had continuous glucose monitoring for 72 hours on 2 separate occasions. 22% of people on sulphonylureas and 20% of people on insulin were recording glucose values less than 2.2mmol/l for more than 20 min! This study was funded by the Dept for Transport! The risk of hypoglycaemia with sulphonylureas is real, significant and potentially dangerous. Your document, I believe, underestimates the risk as it relies on clinical trials where patients tend to be fitter and with better follow-up. The problem is particularly serious in the elderly and in those with renal impairment. In these groups, in particular, sulphonylureas should be used with great caution, if at all.	Noted. This study was published before SIGN 116 and is therefore outwith the literature review date for this guideline. The absolute and relative risks of hypoglycaemia associated with sulphonylureas compared with other options are clearly defined in this section. However we recognise that in many instances RCT outcomes might not reflect the use of a particular medication in the real world and have highlighted this in the Provision of Information section.
	FG	Rate of ‘major hypo’ in reference 24 seems very high compared to clinical experience? Reference 26 – conflating weight gain and hypo in this elderly population not necessarily helpful.	The study (ref 24) cites ‘severe’ hypo with metformin or diet as 0.05/per 100 patient years compared with 0.9/100 patient years for SUs. This sentence reports the results of the study. The study outcome was “achievement of HbA1c <7.0% without hypoglycaemia or weight gain”.
	RCP	Comprehensive.	Thank you. Noted.
	JM	Satisfactory.	Thank you. Noted.
	SM	Given the evidence for hypoglycaemia risk especially in those over 65 years who form a substantial number of those with type 2 diabetes, should the recommendations for use not be reversed and a caution included for age?	Higher risk of hypoglycaemia with sulphonylureas in the elderly is flagged in the Provision of Information section.

	AZ	With respect to agents in the SGLT2 inhibitor class, it is not clear why only canagliflozin's trial is highlighted when all three SGLT2 inhibitors are recommended in this position. We propose that dapagliflozin and empagliflozin trials are referred to for completeness/balance. For dapagliflozin please refer to: Dapagliflozin v Glipizide as Add-on Therapy in Patients with Type 2 Diabetes Who Have Inadequate Glycaemic Control with Metformin A randomized, 52-week, double-blind, active-controlled non-inferiority trial. In this RCT the primary end-point, adjusted mean HbA1c reduction was statistically non-inferior at 52 weeks for dapagliflozin (-0.52%) compared with glipizide (-0.52%), Key secondary end points: dapagliflozin produced significant adjusted mean weight loss (-3.2 kg) versus weight gain (1.2 kg; p<0.0001) with glipizide, significantly increased the proportion of patients achieving ≥ 5% body weight reduction (33.3%) versus glipizide (2.5%; p<0.0001), and significantly decreased the proportion experiencing hypoglycaemia (3.5%) versus glipizide (40.8%; p<0.0001). Reference: *Nauck et al Diabetes Care 2011 34: 2015-2022 2011. DOI: 10.2337/dc11-0606*	This study was identified in the SIGN literature searches, but is included in the AHRQ meta-analyses therefore not included separately in the SGLT2 section. The AHRQ review has not been cited as evidence for glycaemic lowering for SU (evidence from SIGN 116 being retained).
	MSD	MSD commends the guideline development group (GDG) for including robust analyses on hypoglycaemia adverse effects as well as cardiovascular morbidity and mortality. In addition, MSD would like to bring to the attention of the GDG an observational study conducted to investigate the risk of severe hypoglycaemia, fatal and non-fatal CVD and all-cause mortality associated with the combination treatment with either sulfonylureas and DPP-4 inhibitors with metformin. The study comprised of 52,760 patients; divided into two cohorts. One cohort was started metformin + SU and the other cohort metformin + DPP-4i. The incidences for severe hypoglycemia, CVD, and all-cause mortality in the SU cohort were 2.0, 19.6, and 24.6 per 1000 patient-years whilst in the DPP-4i cohort were 0.8, 7.6, and 14.9 per 1000 patient-	Thank you. The new systematic literature searches were limited to RCTs. Some older observational studies are carried over from the previous version of the guideline.

		years, respectively. The results which were statistically significant showed that sulfonylureas when compared with DPP4i was associated with a higher risk of subsequent severe hypoglycemia, fatal and nonfatal CVD, and all cause mortality; adjusted HR (95% CI): 2.07 (1.11–3.86); 1.17 (1.01–1.37); and 1.25 (1.02–1.54), respectively. Reference: *Eriksson JW, Bodegard J et al. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. Diabetes Research and Clinical Practice 2016; 117:39-47*	
5.3	AG	Carefully researched and presented.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	ABI/EL	GRADE & CAROLINA study acronyms could be used as in keeping with style of whole draft guideline and to help orientate readers with the large number of landmark studies in T2D.	Agreed – acronym has been added although GRADE has now been removed.
	SB	P13. It is not clear to me where the first recommendation for SUs as alternative first-line agents to metformin comes from?	This recommendation was retained from SIGN 116.
	FG	ADOPT MI data 2 v 3 events (Ref 2) – small numbers to base conclusion on. Is GRADE designed to look at CV outcomes? (Ref 32) – it is primarily a glycaemic study and perhaps not powered to look at CV outcomes. RECOMMENDATIONS: Considered as 1st line in people who are not overweight – isn't this just wrong – metformin works just as well?	Agreed. This has been further highlighted in the text "Although 4,360 individuals were randomised, *absolute event rates were very low*…" Agreed. GRADE has been removed. Agreed. This has been revised.
	SMac	Agreed.	Thank you.
	RCP	Clear.	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
	MSD	MSD commends the guideline development group (GDG) for including robust analyses on hypoglycaemia adverse effects as well as cardiovascular morbidity and mortality. In addition, MSD would like to bring to the attention of the GDG an observational study conducted to investigate the risk of severe	Thank you. The new systematic literature searches were limited to RCTs. Some older observational studies are carried over from the previous version of the guideline.

		hypoglycaemia, fatal and non-fatal CVD and all-cause mortality associated with the combination treatment with either sulfonylureas and DPP-4 inhibitors with metformin. The study comprised of 52,760 patients; divided into two cohorts. One cohort was started metformin + SU and the other cohort metformin + DPP-4i. The incidences for severe hypoglycemia, CVD, and all-cause mortality in the SU cohort were 2.0, 19.6, and 24.6 per 1000 patient-years whilst in the DPP-4i cohort were 0.8, 7.6, and 14.9 per 1000 patient-years, respectively. The results which were statistically significant showed that sulfonylureas when compared with DPP4i was associated with a higher risk of subsequent severe hypoglycemia, fatal and nonfatal CVD, and all cause mortality; adjusted HR (95% CI): 2.07 (1.11–3.86); 1.17 (1.01–1.37); and 1.25 (1.02–1.54), respectively. Reference: *Eriksson JW, Bodegard J et al. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. Diabetes Research and Clinical Practice 2016; 117:39-47*	
	NHSsig	Typing error sentence “All three cohort studies higher risk reported a higher risk...” Delete duplicated higher risk.	Thank you. This has been corrected
Section 6			
General	RCPL	Pioglitazone and bladder health - state as not an issue based on recent info.	Current SmPC states that bladder cancer is a risk for patients taking pioglitazone, despite recently published evidence. The updated guideline refers to the FDA statement (December 2016) and recent meta-analysis by Li et al (Int J Clin Pharmacol Ther, 2017. 55(3); 210-219.
	AB	In your recommendations/cautions you mention making patients aware of certain increased risks but you don’t mention heart failure. There is also a caution in the licence re bladder cancer.	Thank you for your comment. There is a recommendation that pioglitazone should not be used in patients with heart failure. With regard to bladder cancer the updated guideline refers to the FDA statement (December 2016) and recent meta-analysis by Li et al (Int J Clin Pharmacol Ther, 2017. 55(3); 210-219. A note has also been added to the algorithm.
	MF	Recommendations for Pio are fine.	Thank you. Noted.

	FG	Any mention of potential NAFLD benefit? Any data to support TZD in higher BMI – what weight threshold?	Thank you for your comment. While there are some data suggesting improved liver histology following pioglitazone treatment in patients with NASH, this was not a pre-specified outcome of the literature searches. Of note, the recent EASL-EASD-EASO guidelines do not currently endorse this as a therapeutic strategy and we have therefore not included this in the SIGN update. The data we have reviewed all point towards weight gain and oedema in patients treated with pioglitazone and we therefore have not made specific recommendations for use in patients with high BMI. The literature review did not identify any studies which stratified treatment by weight.
	RCPE	There is no mention of TZD withdrawal with macular oedema. We are surprised there is no mention of risk of bladder cancer in relation to pioglitazone.	Thank you for your comments. AHRQ did not identify any moderate or high-quality evidence for macular oedema associated with any drug. BNF does not specifically list macular oedema as a caution or contraindication for treatment, though both “oedema and visual disturbance are listed as common or very common side effects.” Agreed. The updated guideline refers to the FDA statement of December 2016 and the meta-analysis by Li et al (Int J Clin Pharmacol Ther, 2017. 55(3); 210-219. A note has also been added to the algorithm.
	JM	Satisfactory. It is good to see this section updated significantly.	Thank you. Noted.
	JN	“Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c in combination with metformin, sulphonylureas, DPP-4 inhibitors or insulin.” Janssen and Napp believe that both canagliflozin and empagliflozin should be included in this recommendation as they both are licenced for use with pioglitazone References: *Canagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28400 (last accessed 22/05/2017)*	Thank you for your comment. The draft has been updated to reflect that some agents are also licensed for use with pioglitazone.

		Empagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28973 (last accessed 22/05/2017) 4.1 Therapeutic indications Invokana is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: • Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. • Add-on therapy Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies). 5.1 Pharmacodynamic properties; Placebo-controlled studies Canagliflozin was studied as monotherapy, dual therapy with metformin, dual therapy with a sulphonylurea, triple therapy with metformin and a sulphonylurea, triple therapy with metformin and pioglitazone, and as an add-on therapy with insulin (table 2). In general, canagliflozin produced clinically and statistically significant ($p < 0.001$) results relative to placebo in glycaemic control, including HbA1c, the percentage of patients achieving HbA1c < 7%, change from baseline fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG). In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.	
	SMC	The last sentence of the first paragraph should read “Pioglitazone is now the only TZD with a marketing authorisation.”	Thank you. This revision has been made.
6.1.1	AG	Trial data well presented and accurate.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
	DS	Indicate Pioglitazone as an option for monotherapy when other therapies such as Metformin, Sulphonylurea etc are contraindicated or tolerated	A sentence has been added to summarise the SMC status of pioglitazone monotherapy.
	EL	AWARD-1: Please refer to additional information document	Thank you for your comment. AWARD 1 has been excluded due to too few patients in the placebo group (a

			prespecified exclusion criteria for this guideline). The draft guideline has been updated and now indicates that GLP-1 agents are licensed for use with pioglitazone.
6.1.2	AG	I wonder whether more emphasis should have been placed on adverse effects which, to many clinicians, vastly outweigh any positive effect of this therapy.	Thank you for your comment. Agreed. The updated guideline has been revised to refer to the FDA statement of December 2016 and the meta-analysis by Li et al (Int J Clin Pharmacol Ther, 2017. 55(3); 210-219. A note has also been added to the algorithm.
	AB	Agreed	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
	DS	There is a need to add bladder cancer as an increased risk associated with the use of Pioglitazone.	Thank you for your comment. Agreed. The updated guideline has been revised to refer to the FDA statement of December 2016 and the meta-analysis by Li et al (Int J Clin Pharmacol Ther, 2017. 55(3); 210-219. A note has also been added to the algorithm.
6.1.3	AG	Presented in accordance with the appropriate trial data.	Thank you. Noted.
	AB	Agreed	Thank you. Noted.
	JM	Satisfactory	Thank you. Noted.
6.2	AG	Not used, not sure it should have been included at all in the guideline.	Thank you for your comment. The decision was taken that the safety information about rosiglitazone should remain within the update as this section of SIGN 116 will no longer be available to view following publication of the update. Further, the change in licence since the previous guideline warrants its inclusion, along with the differences in regulatory approaches taken by EMA and FDA.
	AB	Agreed	Thank you. Noted.
	SMac	Interesting, is there likely to be marketing authorisation applied for again in UK in future?	While the GDG is not aware of any current application of this type, due to the availability of rosiglitazone under specific circumstances in the USA, it remains theoretically feasible that the drug may re-enter the formulary in future.
	JM	Satisfactory	Thank you. Noted.
Section 7			
General	RCPL	Info on saxagliptin CCC.	We don't understand this comment.
	AB	I don't understand why you mention sulphonylureas as a monotherapy alternative to metformin but not DPP-4 inhibitors. This class has equivalent efficacy but much lower risk of	The following has been added "Linagliptin, sitagliptin and vildagliptin are accepted for use as monotherapy by SMC. These should be considered for

		hypoglycaemia or weight gain. Even NICE has recommended DPP-4 inhibitors first line in these circumstances! You might also think about SGLT2 inhibitors in a similar context.	use in those for whom both metformin and sulphonylureas are inappropriate due to contraindications or intolerance."
	ABI/EL	GIP should be added as DPP-4s prolong actions of both GLP-1 & GIP.	Although this is a known effect of the drug, the GDG do not feel that this level of detail is required for the general reader.
	MF	Recommendation for DPP-4i is fine. Could add a good practice point about use in the elderly (>70 years) as second line instead of sulphonylureas to reduce the risk of hypoglycaemia.	Higher risk of hypoglycaemia with sulphonylureas in the elderly is flagged in the Provision of Information section.
	RCP	Overall well written and presented section, clear presentation.	Thank you.
	NG	Worthwhile commenting on DPP 4 inhibitors and SGLT2 inhibitors as a combined preparation is available. Even if it is not recommended, then this should be commented on.	No evidence was identified for this combination. Other than the fixed-dose combination, the DPP4 inhibitors are only licensed for triple therapy with metformin plus sulphonylureas.
	ME	Some consideration to potential budget impact implications of different agent acquisition cost would be of use in terms of informing therapy choice	SMC provides budget impact advice for all approved drugs. As this is a constantly changing issue, the reader is directed to the SMC website for the latest advice.
	JM	Satisfactory	Thank you.
	Sa	For insulin glargine, please ensure that the appropriate glargine is included (U100 or U300).	Thank you – the concentration has been clarified wherever insulin glargine is specifically mentioned.
	DS	Indicate DDP-4 inhibitors as an option for monotherapy when other therapies such as Metformin, Sulphonylurea etc are contraindicated or tolerated	No evidence for DPP-4 inhibitors as monotherapy was reviewed, however, this option has been noted in section 7.1 of the revised draft and included in the algorithm.
	MSD	MSD commends the robustness of this section. A concern MSD has is the difference in licence indications for each drug within this class. MSD feels the GDG has not made adequate differentiation between each drug within the class to enable more informed decisions from prescribers. According to the draft guideline (page 3); "off label prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the market authorisation". As there is at least one DPP4i that is licensed for each intensification step and in each relevant combination MSD feels that in this case, omission of this detail may lead to inappropriate prescribing. The table	Thank you. The wording of the recommendation "usually as dual or triple therapy" covers the scenario that DPP4 inhibitors may be used as monotherapy in some individuals intolerant of metformin and SUs. For linagliptin and vildagliptin this will be not be off-label but the SIGN guideline is not a stand-alone document: prescribers are also referred to SMC advice for further information.

		provided separately documents the licence indications. MSD also suggests the SMC guidance and restrictions on the various DPP-4 inhibitor agents be highlighted to further improve decision making. According to SMC guidance: • saxagliptin is confined for use as triple therapy in combination with metformin and sulfonylurea • alogliptin is approved for use as dual therapy alone • linagliptin is approved for use as monotherapy, dual and triple therapy • vildagliptin is approved for use as monotherapy • sitagliptin is approved for use in dual and triple therapy References: *Sitagliptin Summary of Product Characteristics. EMC. January 2016. http://www.medicines.org.uk/emc/medicine/19609; accessed February 2017* *Vildagliptin Summary of Product Characteristics. EMC. December 2015. http://www.medicines.org.uk/emc/medicine/20734; accessed February 2017* *Saxagliptin Summary of Product Characteristics. EMC. April 2016. http://www.medicines.org.uk/emc/medicine/22315; accessed February 2017* *Linagliptin Summary of Product Characteristics. EMC. January 2017. http://www.medicines.org.uk/emc/medicine/25000; accessed February 2017* *Alogliptin Summary of Product Characteristics. EMC. January 2015. http://www.medicines.org.uk/emc/medicine/28513; accessed February 2017*	
	JN	"DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c in combination with metformin, sulphonylureas, thiazolidinedione's or insulin" The SmPC does not include any statements on restrictions for the use of canagliflozin with other glucose-lowering medicines. Therefore, it can be considered within licence when added-on to any other anti-hyperglycaemic agent, including DPP-4 inhibitors. Reference: *Canagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/2*	The statement has been revised to "DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c."

		8400 (last accessed 22/05/2017) • 4.1 Therapeutic indications Invokana is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. Add-on therapy Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies). *Fulcher et al. Efficacy and safety of canagliflozin when used in conjunction with incretin mimetic therapy in patients with type 2 diabetes. Diabetes Obes Metab. 2015 Oct 9. doi: 10.1111/dom.12589.*	
	NHSLot	The section on DPP-4 inhibitors could also be qualified with some expert guidance. Although non-inferiority studies show the DPP-4 inhibitors to be comparable to metformin or sulphonylureas, individual monotherapy trials consistently show that DPP-4 inhibitors do not lower HbA1 as much as other oral hypoglycaemic agents. They are widely accepted within clinical practice to be the gentlest glucose-lowering agents available. On page 16, in the second paragraph of section 7.1, I assume it should read that "the authors note that their meta-analyses may have OVER-estimated [rather than underestimated] the HbA1c reduction with the metformin and DPP-4 combination…"	Thank you. This guideline does not specifically recommend these agents for monotherapy, though highlights that they may be considered in the situation of intolerance to metformin and sulphonylureas. This comment is consistent with the guideline which states that DPP4 inhibitors lower HbA1c more than placebo, but less than metformin. The SIGN guideline is not a stand-alone document: prescribers are also referred to SMC advice for further information. Thank you. This typo has been corrected. The comment in the AHRQ document refers specifically to the comparison MF+DPP4 vs MF+TZD – this has also been clarified.
7.1	AG	Perhaps more emphasis placed on the fact these agents are not as potent as the others available. This information is available but somewhat embedded within the text.	This information has been expressed in the algorithm which notes their glucose-lowering efficacy as moderate/low.
	AB	Agreed	Thank you
	ABI/EL	First sentence: please include linagliptin. This section should include data on Linagliptin monotherapy when metformin	We are aware that SMC has accepted linagliptin for monotherapy in restricted circumstances and have added a

		is inappropriate *Barnett et al. Diabetes ObesMetab. 2012 Dec;14(12):1145-54. doi: 10.1111/dom.12011. Epub 2012 Oct 1.* Trajenta SMC advice available to support this use. Linagliptin add on to metformin + empagliflozin new data now available.	paragraph to summarise this. We have mentioned this as a note in the algorithm. The trial evidence does not add any significant new information to the overall body of evidence and has not been included. This combination is possible within the algorithm.
	SB	P16. 'However, the authors note that their meta-analyses may have underestimated HbA1c reduction with the metformin and DPP-4 combination as some studies did not use optimal doses of comparator drugs' - this seems to be the wrong way around? Wouldn't the HbA1c lowering be over-estimated?	We agree that this is a typo which has been corrected. The comment in the AHRQ document refers specifically to the comparison MF+DPP4 vs MF+TZD – this has also been clarified.
	FG	Are network meta-analyses conclusions robust? (Thinking of NICE conclusions based on this methodology – re repaglinide!)	NICE may have included some low-quality studies in their repaglinide NMA as their exclusion criteria were less stringent than those used by SIGN. This does not invalidate the approach provided its limitations are appreciated and made explicit.
	RCPE	DPP4i are recognized clinically as poor drugs in patients with longer duration of diabetes. As a group they are the least effective antidiabetic agents. There is no mention of DPP4i and renal dysfunction with change in dosage.	This population factor was not searched for, specifically, therefore we have not identified evidence which supports or refutes this opinion. The SIGN guideline is not a stand-alone document: prescribers are also referred to advice from SMC and the BNF. This is covered for CKD Stage 3A in the algorithm.
	JM	Satisfactory. Just one comment regarding the word of caution at the end of paragraph 2 regarding HbA1c reductions. This leaves the reader slightly wondering what they are meant to take from the preceding sentences. It would be good if something more definite could be concluded rather than be vague.	We agree that this is a typo which has been corrected. The comment in the AHRQ document refers specifically to the comparison MF+DPP4 vs MF+TZD – this has also been clarified.
	Ta	1. The evidence base focuses on sitagliptin, vildagliptin and saxagliptin. However, as described in section 7.0, there are two other DPP-4 inhibitors available, alogliptin and linagliptin. We recommend that further evidence is added for these additional DPP-4 inhibitors. As the manufacturer for alogliptin, we would like you to consider the following summarised data. Indication	

		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 can be used in combination with other therapies, e.g. in dual therapy, triple therapy, or with insulin.	Evidence is included in section 5.2 for superiority of alogliptin over SU (in the SU section), but low quality. However, most studies provided by the reviewer are outwith the search period for the evidence review (ie, they predate SIGN 116).
		Clinical data • Alogliptin improves glycaemic control in combination with other glucose lowering treatments for adults with T2DM (1-6) • At 26 weeks, alogliptin is associated with an average reduction in HbA1c of between 0.50.9% (5.59.8 mmol/mol) from baseline when added to metformin, an SU, pioglitazone or insulin(1-6) • When added to metformin, alogliptin demonstrated a durable reduction in HbA1c levels that was statistically superior to a sulphonylurea plus metformin (glipizide, mean dose 5.2 mg) at 2 years(6) • In a post hoc analysis of the EXAMINE CV Safety Trial, alogliptin in triple therapy with metformin and a sulphonylurea appeared to be well tolerated, and provided significant reductions in HbA1c (LS mean difference for change from baseline of HbA1c at last visit -0.52% ($p<0.001$))(7) •Alogliptin provides similar HbA1c reductions in older (≥65 years) and younger patients (<65 years) with no differences seen in the safety profile(8)	Thank you for these comments. The summary of evidence is generally intended to convey evidence about the class rather than its specific members, which are all mentioned. We focused on agents for which evidence was identified in the period of our literature search.
		References: *1. Nauck MA, et al. Int J Clin Pract 2009; 63: 46-55.* *2. Pratley RE, et al. Curr Med Res Opin 2009; 25(10): 2361-2371.* *3. Pratley RE, et al. Diabetes Obes Metab 2009; 11(2): 167-176.* *4. Rosenstock J, et al. Diabetes Obes Metab 2009; 11: 1145-1152.* *5. Bosi E, et al. Diabetes Obes Metab; 2011; 13(12): 1088-1096.* *6. Del Prato S, et al. Diabetes, Obes Metab 2014; 16 (12): 1239-1246* *7. Heller S et al. Presented at the American Diabetes Association, 76th Scientific Sessions, June 10–14, 2016, New Orleans, LA.* *8. Pratley RE, et al. J Am Geriatr Soc 2009; 57(11): 2011-2019*	References 1-4 and 8 are outwith search period. Reference 5 was outwith the scope of AHRQ. Reference 6 was identified but appraised as too low quality to use as evidence. Reference 7 is a conference presentation and not eligible.

		2. Paragraph 2 in this section states that the HbA1c reduction seen with a DPP-4 inhibitor is less than that seen with an SGLT2 inhibitor (pooled between group difference 0.17%, 95% CI 0.08%-0.26%), taken from the AHRQ systematic reviews and meta-analyses published in 2016. Although there is a caveat added to this statement that "the authors note that their meta-analyses may have underestimated HbA1c reduction with the metformin and DPP4 inhibitor combination as some studies did not use optimal doses of comparator drugs", this data is cited with a 1++ level of evidence. However, the AHRQ review included only four studies in combination therapy comparing these classes of therapy, all of which did not include any patients with renal impairment (which may have an effect on the efficacy of an SGLT2 inhibitor) and were short in duration (12-24 weeks). This potentially introduces a risk of bias which reduces the level of evidence that should be applied to this statement. The ADA/EASD consensus statement on the management of Type 2 diabetes states that the efficacy of both of these classes is "intermediate". We recommend that the evidence rating is adjusted to 1- accordingly and the statement that efficacy with a DPP-4 inhibitor being less than that of an SGLT2 inhibitor being amended to the efficacy of a DPP-4 inhibitor may be less than that of an SGLT2 inhibitor.	
	AZ	It is not clear why only canagliflozin's data is mentioned in this section when all three SGLT2 inhibitors are recommended in this position. We suggest that dapagliflozin and empagliflozin trials are also referred to for completeness/balance. For dapagliflozin please refer to: 1. Dapagliflozin as Add-on Therapy to Sitagliptin With or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Baseline HbA1c and FPG levels were 7.9% (63.0 mmol/mol) and 162.2 mg/dL (9.0mmol/L) for the dapagliflozin group and 8.0% (64.0mmol/mol) and 163 mg/dL (9.0 mmol/L) for placebo. At week 24, dapagliflozin significantly reduced mean HbA1c levels (–0.5% [–4.9 mmol/mol]) versus placebo (0.0% [+0.4 mmol/mol]).	This section is not focused on SGLT2 inhibitors. The single trial comparing sitagliptin with canagliflozin was the only relevant piece of evidence identified with an SGLT2 comparator. Thank you. On review, we found this study to assess the efficacy and safety of dapagliflozin in patients whose HbA1c levels were not adequately controlled with sitagliptin, rather than providing evidence for the use of the DPP4 inhibitor, and therefore have not included it..

		Dapagliflozin reduced body weight versus placebo (–2.1 and –0.3 kg). Reference: *Jabbour et al Diabetes Care 37 March 2014* 2. In a post hoc analysis comparing the saxagliptin arm and dapagliflozin arm from a double-blind trial in T2D adults with HbA1c ≥ 8.0% and ≤ 12.0% (64108 mmol/mol). The patients were randomized to saxagliptin (SAXA) (5 mg od) plus dapagliflozin (DAPA) (10 mg od; n=179), or SAXA (5 mg od) and placebo (n=176), or DAPA (10 mg od) and placebo (n=179) on background metformin extended release (MET) ≥1500 mg/day for 24 weeks Summary of Data: Treatment with dapagliflozin compared to saxagliptin resulted in an adjusted mean change from baseline of -0.32% in A1c (95% CI 0.10 to 0.54), demonstrating statistical superiority (p=0.004) after 24 weeks of treatment. Reference: *Poster 99 Presented at the 14th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC), Los Angeles, CA, USA; Supported by: December 1–3, 2016*	Evidence from posters is not eligible for inclusion in SIGN guidelines.
	NHSsig	Table 1 in the AHRQ includes a meta-analysis of Su vs DPP4 HbA1c in favour of SUs which is not referenced. The statement regarding the Network meta-analysis of HbA1c benefit of vildagliptin over metformin at 24 months should also reference that both pioglitazone & SU were ranked higher than vildagliptin at 24 months. (NICE Table 51 pg 179 full guide). Please check the statement “However the authors note that their meta-analysis may have underestimated HbA1c reduction with the metformin & DPP4 combination as some studies did not use optimal doses of comparator drugs.” AHRQ - when the DPP4 combination is compared to TZD & SU comparators it is	Agreed. This is an oversight. We have included this. Noted. The interpretation of the data does not lead us to recommend DPP4 inhibitors as first line therapy. We also do not recommend pioglitazone as monotherapy. For consistency, the TZD recommendation has been revised to “Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c” We agree that this is a typo which has been corrected. The comment in the AHRQ document refers specifically to the comparison MF+DPP4 vs MF+TZD – this has also been clarified.

		TZD & SU that are underdosed or of moderate dose which implies it is the comparators HbA1c reduction that is underestimated not the DPP4 combo.	
	JMc	'the authors note that their meta-analyses may have underestimated HbA1c reduction with the metformin and DPP-4 combination as some studies did not use optimal doses of comparator drugs.' Comment – should this not be overestimated. Are you using mol/mol or % as first description for HbA1c suggest mol/mol e.g. tables for gliflozins	Agreed. This typo has been revised We believe that most clinicians will recognise % more readily than mmol/mol. Following other consultation comments, Table 2 has been removed.
	ABPI	There is evidence for the use of DPP-4s in conjunction with SGLT2's and therefore this should be reflected in the recommendations.	This evidence (Søfteland et al, 2017) was published after the literature search. In addition, insufficient numbers of participants were randomised to fulfil prespecified inclusion criteria.
	EL	AWARD 5: Please refer to additional information document.	Thank you. This study is included in the AHRQ review. It shows greater HbA1c lowering with dulaglutide than sitagliptin at 52 weeks which is consistent with the current guideline content.
7.2	AG	Appropriate.	Thank you
	AB	Agreed	Thank you
	JM	Satisfactory.	Thank you
	AZ	It is not clear why only empagliflozin data is mentioned in this section when all three SGLT2-inhibitors are recommended in this position. We suggest that dapagliflozin and canagliflozin trials are referred to for completeness/balance. For dapagliflozin please refer to: 1. In a post hoc analysis comparing the saxagliptin arm and dapagliflozin arm from a double-blind trial in T2D adults with HbA1c ≥8.0% and ≤12.0% (64-108 mmol/mol). The patients were randomized to saxagliptin (SAXA) (5 mg od) plus dapagliflozin (DAPA) (10 mg od; n=179), or SAXA (5 mg od) and placebo (n=176), or DAPA (10 mg od) and placebo (n=179) on background metformin extended release (MET) ≥1500 mg/day for 24 weeks Summary of Data: Treatment with dapagliflozin compared to saxagliptin resulted in an adjusted mean change from baseline of -0.32% in A1c (95% CI	This was the only trial identified in the AHRQ review comparing weight outcomes for DPP4 inhibitors and SGLT2 inhibitors. This section is not focused on SGLT2 inhibitors. The single trial in the AHRQ review comparing sitagliptin with empagliflozin was the only relevant piece of evidence identified with an SGLT2 comparator.

		0.10, 0.54), demonstrating statistical superiority (p=0.004) after 24 weeks of treatment. The statistical superiority of dapagliflozin vs saxagliptin at week 24 was also demonstrated for weight loss (-2.39 kg vs 0.0 kg; p<0.0001) Reference: *Poster 99 Presented at the 14th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC), Los Angeles, CA, USA; Supported by: December 1–3, 2016*	Evidence from posters is not eligible for inclusion in SIGN guidelines.
7.3	AG	Good review of studies to date and a good outcome summary.	Thank you
	AB	Agreed	Thank you
	ABI/EL	No mention of CARMELINA (linagliptin CV safety study vs placebo) in this draft whereas other ongoing CV safety studies are mentioned, eg DECLARE.	Agreed. We have added a reference to this ongoing study.
	SB	P17. 7.3. I think it would be useful to mention the HbA1c differences between the active and placebo-treated groups in the DPP-4 CVOTs.	Thank you. We disagree with this suggestion. Glycaemic efficacy is best assessed against specific comparators in earlier phase studies as we have summarised, rather than against standard of care which may involve heterogeneous comparators. For consistency we have removed the HbA1c reduction data of the CVOTs from the GLP-1 section (ie moved information from sections 8.1.1 to 8.3 in the revised version).
	FG	RECOMMENDATION: These drugs are less effective than SGLT2 and GLP1 agents, shouldn't the recommendation reflect this? Should we really be using these drugs with insulin – weak evidence? Treating to target morning glucose of 6.1mM / 5.6mM – this does not reflect real clinical practice. Setting up a hypoglycaemia 'straw man' to demonstrate efficacy of new medication.	The evidence summary and algorithm together provide more information rather than the recommendation alone which directs healthcare professionals to appropriate action. The recommendation has been altered to: "DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c."
	SMac	Agreed.	Thank you
	Ta	It is reassuring to see the EXAMINE outcomes included within this section. In relation to heart failure, we recommend that direction to the EMA licensed recommendations is added to aid the	Noted. The evidence summarised in a SIGN guideline is primarily an evidence-based review of the published literature,

		reader in their decisions. Following their review of the EXAMINE data, the EMA added no additional warnings on HF to the alogliptin SmPC. Conversely the warnings for use in NYHA Class III and IV were downgraded following the review of the EXAMINE study findings, from "Not recommended" to "Caution is warranted" due to limited experience.	referring the reader to updated guidance from regulatory bodies rather than comprehensively summarising them. The guideline is not "stand alone". Prescribers should refer to advice from SMC, BNF and MHRA.
	SMC	Suggest removing "(i.e safety)" from the second paragraph in this section. The composite endpoint is described and would not necessarily be considered a "safety" outcome, since this was the primary objective of the study. Safety endpoints are generally secondary outcomes and refer to adverse events.	Agreed. Revision has been made.
	JM	Satisfactory.	Thank you
	MSD	In addition to the evidence presented within the cardiovascular and morbidity section relating to the use of DPP4I's. MSD would like to further highlight the findings of TECOS (Trial Evaluating Cardiovascular Outcomes for Sitagliptin), which further demonstrates that there may not be complete alignment/ interchangeability between agents within the DPP4 class… The guideline correctly states the "rates of hospitalisation for heart failure were almost identical with sitagliptin versus placebo over three years in the TECOS study (HR 1.00; 95% CI, 0.83 to 1.20; P=0.98)". MSD believes this does not give the full scope of the conclusions to be made from these results. MSD suggests that a potential explanation for the results reported in TECOS is intrinsic pharmacological differences between the DPP-4 inhibitors. This information would prove useful to prescribers to highlight the variability between agents in this class.	The evidence cited is summarised for the reader but based on SIGN methodology there is insufficient evidence to go further than that. The suggestion that there is an intrinsic pharmacological difference among DPP-4 inhibitors is only one potential plausible explanation for the results of the clinical trial.
Section 8			
General	AG	Very rarely used. Useful to include the agent and glycaemic control, hypoglycaemic/weight gain/adverse effects commentary apposite.	Noted. Thank you. Following consideration of the consultation comments, the entire section on alpha-glucosidase inhibitors has been removed from the guideline.
	AB	Note the very high incidence of side-effects with these agents and extremely poor adherence. Suggest change your recommendation to "Acarbose CAN be considered....but note the very high	See above

		incidence of gastro-intestinal side-effects can be a major issue"	
	SB	"Acarbose should be considered for glycaemic control in people with type 2 diabetes." is the broadest endorsement given for any pharmacotherapy in this guideline and yet it is only used in a few % (probably less than 1%) in the UK. Given that this guideline is aimed at such a wide constituency, surely this reality gap needs to be addressed?	See above
	MF	Recommendation for acarbose could be removed. This drug is seldom used in UK/Scottish practice (this comment could be added). Removing a rec for acarbose simplifies the number of choices for second line and third line.	See above
	FG	Is this section needed? Does anyone in the UK use these? Misleading to suggest tolerability similar to metformin?	See above
	JM	Satisfactory.	Noted, thank you.
	DS	It would be helpful to provide clear guidance to indicate whether Acarbose should be used as mono, dual, and/or triple therapy.	See above
	NHSLot	The section on acarbose is not consistent with current practice. The recommendation that acarbose should be considered for use in type 2 diabetes does not give the non-specialist any guidance as to where it should be placed on the therapeutic ladder. Although studies suggest a similar rate of GI side effects to metformin, my understanding is that it is a very poorly tolerated agent. The committee could consider a good practice point to the effect that therapy is frequently associated with GI side effects.	See above
8.1	AG	See above.	Noted, thank you.
	AB	Agreed.	Noted, thank you.
	RCPE	The inclusion of Alpha-glucosidase inhibitor inclusion is surprising as there are very few patients on this class of drug because of side effects.	See above
	JM	Satisfactory.	Noted, thank you.
	AZ	Given the evidence base, AstraZeneca propose the recommendation is altered (in line with the existing guideline) to: “Acarbose can be used as an option in monotherapy if other options such as metformin, sulphonylurea or SGLT2-	See above

		inhibitors are not tolerated or are contraindicated."	
8.2	AG	See above.	Noted, thank you.
	AB	Agreed.	Noted, thank you.
	JM	Satisfactory.	Noted, thank you.
Section 9			
General	RCPL	Info on combo GLP1 and SGLT2i. Role of noon RCT data from national audits - eg ABCD audits on GLP1 analogues and dapagliflozin.	No evidence was identified from the literature sources with this comparison. Audit data cannot provide evidence for clinical effectiveness according to SIGN methodology. .
	AG	A busy section with lots of trial data looked at. The trial data presented appropriately with sensible recommendations given. I wonder if more could have been made of LEADER given our 'Holy Grail' for medication is one which improves glycaemic control and cardiovascular morbidity.	Thank you. We have clarified the recommendation to include a similar statement as for SGLT2 inhibitors "In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used".
	FG	Would it be worth mentioning the influence of duration of diabetes upon efficacy (+/- role of C-peptide assessment)? Ref: *10.2337/dc15-0258*	Disagree. GLP-1 agonists have modes of action which are independent of endogenous insulin. The GDG noted that the duration of diabetes in the LEADER study was on average >10 years.
	BK	Overall very good and comprehensive. I would have thought that there is enough evidence to recommend specific GLP-1s given the varying evidence base within that class. There is no recommendation to use a GLP-1 receptor agonist with evidence of cardiovascular benefit when starting this type of drug in overweight patients with established CV disease (as was recommended for SGLT2 inhibitors).	Agree. We have clarified the recommendation to include a similar statement as for SGLT2 inhibitors "In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used".
	RCP	Well presented section.	Thank you
	RCPE	There is mention of CV protection with SGLT2i but not with GLP analogues. Data is available on this from a number of studies and more are coming out soon. This section therefore needs futureproofed. For example, LEADER demonstrated a superior 13% cardiovascular risk reduction compared to standard treatment of care. There is also no mention that LEADER also showed a 22% reduction in nephropathy - one of the most common complications in T2D.	Thank you. We have clarified the recommendation to include a similar statement as for SGLT2 inhibitors "In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used".
	ME	The main issue with this evaluation	Thank you. We have clarified the

		revolves around the LEADER trial, this CV safety study demonstrated CV outcome benefit with liraglutide as such these data should be considered with respect to determining GLP1 agonist therapy choice as these data differentiate liraglutide vs. Other currently available agents within class	recommendation to include a similar statement as for SGLT2 inhibitors "In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used".
	JM	Satisfactory.	Thank you
	Sa	For insulin glargine, please ensure that the appropriate glargine is included (U100-U300).	Agreed. We have revised all references to glargine.
	Ta	The amount of information included in the glycaemic control section for the GLP-1 agonists class is much greater than that for the other classes, for example for the GLP-1 agonists, the glycaemic control section is split into multiple sections (9.1.1-9.1.5), which is not the case for other agents (e.g. thiazolidinediones, DPP-4 inhibitors). We suggest the information provided in this section for efficacy vs. other classes is consistent with that in other sections.	Noted. The structure represented the volume of evidence identified and the range of comparators. The structure is consistent in terms of reporting glycaemic control, adverse effects and CV outcomes, but we have moved some information between the glucose-lowering and CV benefit subsections.
	NHSsig	Comparator cost effectiveness analysis is missing from the guideline which will be relevant to the algorithm and particularly the cost effectiveness of the GLP1s. NICE continue with the health economic modelling from CG28 even with the audit submission from ABCD for GLP1s. From NICE "The GDG considered that GLP-1 mimetic combinations may be a cost-effective option for people with high BMIs who would require high doses (and therefore costs) of insulin or for whom other treatment options were not tolerated or were contraindicated. The GDG also considered that, in people for whom using insulin would have significant occupational implications, this could have a catastrophic impact on the person's quality of life. As a result, the health economic model might critically undervalue the benefits that would be associated with a treatment that forestalled the need for insulin. However, the GDG noted the high costs of these treatment options and their associated stopping rules that were designed to	The rapid review process did not allow searching for primary economic evidence, however NICE's evidence was available to the group for interpretation. Noted. This guideline retains stopping rules from SIGN 116 and have been more explicit in the algorithm that readers should refer to SMC for formal appraisal of the cost-effectiveness of approved medicines.

		ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the GDG chose to retain the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from CG87. 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, the GDG agreed that, given the lack of cost effectiveness of GLP-1s demonstrated in the health economic modelling, the starting and stopping rules from CG87 should be retained."	
	NHSLot	In the GLP-1 section, semaglutide is not mentioned (eg N Engl J Med 2016 Volume 375(19):1834-1844). I appreciate it does not have SMC approval, but neither does the fixed glargine/lixisenatide combination mentioned at the top of page 21, so in the interests of fairness, semaglutide should probably get a brief mention, even if just to acknowledge its existence given that it is likely to be approved before the next iteration of this guideline. As stated at the start, I believe the cardiovascular safety data needs to be given greater prominence. Empagliflozin and Liraglutide now have convincing evidence of cardiovascular risk reduction, including hard outcomes like a reduction in cardiovascular death. It perhaps needs to be emphasised that the cardiovascular data for liraglutide showed superiority whereas the data for lixisenatide only showed non-inferiority. Arguably, this probably merits a practice point after the recommendation on page 22 to highlight that for patients with established cardiovascular disease, there is evidence that liraglutide would reduce cardiovascular risk. That evidence is not yet present for the other GLP-1 agents and clinicians will appreciate a steer on which agent to prioritise for particular patient group.	Semaglutide does not currently hold a marketing authorisation. The fixed dose insulin glargine/lixisenatide has a marketing authorisation but not SMC approval. The sentence relating to the combination has been removed. The guideline already states that: "A further large cardiovascular outcome trial (ELIXA) demonstrated the cardiovascular safety (non-inferiority) of lixisenatide . . ." We have added a recommendation to provide this steer – "For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered."
9.1.1	AB	Agreed.	Thank you
	SB	THIS IS A SERIOUS ERROR AND WILL MAKE READERs THINK THE GUIDELINE AUTHORS DO NOT UNDERSTAND THE CONCEPT OF DIABETES CVOTs. The inclusion of LEADER and ELIXA trials as 'placebo-	Noted. The CVOTs generally compare the agent of interest with placebo and standard-of-care. The reviewer is correct that this is not the same as a placebo-controlled trial. The sections have therefore been reordered and

		controlled" ignores the trial design where patients in the 'placebo' group also received glucose-lowering therapies so as to aim for (although not necessarily achieve) the same HbA1c target as those given active therapy.	LEADER/ELIXA relocated to section 9.3 (revised numbering).
	FG	Glycaemic efficacy not relevant for LEADER and ELIXA studies. These studies were not assessing glycaemic control and titration to target should have been equal between placebo and active. These references are not relevant to this section and should be removed.	Agreed. See above.
	JM	Satisfactory.	Thank you
	NovNo	The objective of the LEADER CVOT was to show cardiovascular safety of liraglutide in addition to standard therapy and not to show glycaemic efficacy; therefore the investigators adjusted standard of care treatment for both diabetes and other comorbid conditions throughout the trial. Thus we believe that LEADER should be included under section 9.3 and not 9.1.1 as the trial was not a true placebo trial but a CVOT vs standard of care where patients in both arms were treated to target using different therapies including SUs, DPP4i and insulins.(1) Further we would like to suggest that along with the current sections the guidelines include a section comparing use of or switching from GLP-1RA to DPP4i in section 9. These comparisons are clinically important in determining the differences between incretin agents. An example of these studies is the LIRA-SWITCH trial comparing the efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes ((LIRA-SWITCH): a randomized, double-blind, double-dummy, active controlled 26-week trial). In this trial, greater reduction in mean HbA1c was achieved with liraglutide than with continued sitagliptin (-1.14% v -0.54%; estimated mean treatment difference (ETD): -0.61% (95% CI -0.82 to -0.40; p<0.0001)), confirming superiority of switching to liraglutide.(2) *1. LEADER, Marso et al. New Engl J Med 2016;375:311–22* *2. LIRASWITCH,* *Bailey TS et al. Diabetes Obes Metab 2016; 18:1191–1198*	Agreed. See above. Thank you for this comment. Although the GDG was aware of this study, it was published outwith the search period for this guideline. However, the key point (that GLP-1s lower HbA1c more than DPP4 inhibitors) is made clear in the individual evidence summary paragraphs and also the algorithm (which we recognise was not available to the reviewer).

	EL	AWARD-1, AWARD-8, AWARD-9: Please refer to additional information document	SIGN has included newly published CVOTs released during the lifetime of this guideline, but not other studies that report comparisons between classes that have already been included, or different individual drugs within a class already described. The GDG has considered the results of these studies and agreed that, given the general policy to not review each newly published study, these did not warrant inclusion.
9.1.2	AB	Agreed.	Thank you
	JM	Satisfactory.	Thank you
	NovNo	In this section, reference is made to the lack of significant difference in HbA1c between liraglutide and glimepiride seen in a meta-analysis. Please note that the reference in question (Monami et al; reference 64 of the draft clinical guideline) is a meta-analysis of 3 liraglutide studies, including one phase 2 study which didn't use the therapeutic dose of liraglutide (the maximum dose in the trial was 0.75 mg), along with the two phase 3 studies . We therefore think it is incorrect to generalise based on the conclusion of this meta-analysis when comparing the HbA1c-lowering efficacy of liraglutide v sulphonylureas. It is important to note that in the LEAD-3 trial where liraglutide was compared to glimepiride, liraglutide showed a significant difference in HbA1c, with a reduction of -1.2% with liraglutide 1.2 mg and -1.6% with liraglutide 1.8 mg, from baseline, compared to glimepiride which showed an HbA1c reduction of -0.9%. LEAD-3 was a trial comparing liraglutide monotherapy to glimepiride monotherapy for patients with type 2 diabetes (1) *1. LEAD3, Garber A et al. Lancet 2009;373:473–481*	LEAD-3 wasn't included in the evidence tables, due to predating SIGN 116, but does form part of the meta-analysis used in forming the AHRQ data and its conclusions. LEAD-3 is also included in the Monami meta-analysis. The general statement of 'no significant difference' is appropriate within the limits of meta-analysis. *The AHRQ review identified four RCTs comparing sulfonylureas directly with a GLP-1 receptor agonist. Three of the four studies favoured liraglutide over sulphonylureas. AHRQ did not combine these trials in a meta-analysis due to dosing differences between studies. However, only two of the four studies used comparable dosing in the two arms. The first reported no statistically significant differences between the two arms. The second RCT (LEAD-3) favoured the GLP-1 arm. The two other RCTs, lasting 24 and 52 weeks, significantly favoured the liraglutide arm by 0.5% each yet both of these studies used relatively lower doses in the sulphonylurea arm compared with the liraglutide arm, making it difficult to discern drug differences versus dosing differences.* *Therefore, when considered together, the evidence was not considered sufficiently consistent to support a robust and consistent superiority of GLP-1 agonists over sulphonylureas.*
	EL	AWARD-8: Please refer to additional information document	See above
9.1.3	AB	Agreed.	Thank you
	SB	This literature review is out-of-date. Liraglutide has also been directly compared with once-weekly exenatide, once-daily lixisenatide, and the once-weekly GLP-RAs dulaglutide and	These comparisons were not identified in the literature searches for this guideline. The main sources of evidence were SIGN 116, the AHRQ review and NICE guideline, with supplemental searches

		albiglutide. Please update this.	carried out by SIGN. It was felt this would allow a comprehensive review of all agents within class with the most relevant comparators though it is acknowledged that some possible comparisons may not be represented. The comparison between exenatide and liraglutide included in the guideline was carried over from SIGN 116 and neither AHRQ nor NICE include head to head comparisons within class for glucose-lowering drugs. Of the comparisons that the reviewer cites, we note that daily liraglutide is non-inferior to weekly dulaglutide (AWARD-6); once-weekly exenatide was not non-inferior to liraglutide for HbA1c reduction (DURATION-6); once-daily liraglutide is superior to once-daily lixisenatide for HbA1c reduction (Nauck et al 2016) and once-daily liraglutide is superior to once-weekly albiglutide for HbA1c reduction (HARMONY-7). Given that the recommendation will be contingent on choice of agent with proven cardiovascular benefit, the GDG agreed that for conciseness, the increased resource required to appraise these studies would not be offset by the additional information provided.
	FG	There appears to be inconsistent use of p values – present with some CIs and not with others in the document.	p-values which are associated with confidence intervals have been removed in line with Healthcare Improvement Scotland reporting policy. Some p-values are retained in this guideline as they reflect the statistical significance of comparisons between values which are not described with confidence intervals.
	JM	Satisfactory.	Thank you
	AZ	AstraZeneca would like to make the Committee aware of long term data for GLP-1 receptor agonists: 7-year continuous treatment from DURATION-1 (Exenatide Once Weekly). The seven-year extension data from the DURATION-1 study showed sustained HbA1c reduction from baseline over this time with continuous treatment. The improvement in HbA1c from baseline was sustained over seven years, with a mean HbA1c reduction from baseline of -1.1% for the completer population. This sustained effect was observed both in patients who did and those that did not	Evidence from posters is not eligible for inclusion in SIGN guidelines.

		take any new concomitant glucose-lowering medications. The secondary benefit of weight loss from baseline also continued after seven-year continuous treatment. No patients in the ITT population experienced major hypoglycaemia during this period. Reference: *Wysham C. et al. Poster presented at the 76th Scientific Sessions of the American Diabetes Association, June 10-14 2016. New Orleans, LA, United States*	
	NovNo	In addition to the trials mentioned in the guideline, we would also like to highlight that there are a few other within-class comparison trials which have been published. In the LIRA-LIXI trial (Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in T2D: A 26-week randomised clinical trial), at week 26 liraglutide significantly reduced HbA1c (primary end point) more than lixisenatide (ETD -0.62% (95% CI -0.8; -0.4; P<0.0001) (1) In the DURATION-6 RCT (Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes: a randomised, open-label study), at week 26 liraglutide significantly reduced HbA1c (primary end point) more than exenatide once weekly. At the end of the 26-week trial, the change in HbA1c was greater in patients in the liraglutide group (−1·48%, SE 0·05; n=386) than in those in the exenatide group (-1.28%, 0.05; 390) with the ETD (0.21%, 95% CI 0.08 to 0.33; p=0.0018) not meeting the predefined non-inferiority criteria for exanetide (upper limit of CI <0·25%). Patients taking liraglutide lost more weight than did those taking exenatide, irrespective of BMI. At the end of the 26-week trial, the change in bodyweight was greater in patients in the liraglutide group (-3.87kg) with an estimated treatment difference of 0.9kg (95% CI 0.39 to 1.40; p =0.0005) (2) *1. LIRA-LIXI, Nauck et al. Diabetologia (2015) 58 (Suppl 1):OP13-75* *2. DURATION-6, Buse et al. Lancet 2012; 381:9861:117-124*	See above Section 9.1.3 (now 8.1.3) was carried over from SIGN 116. LIRA-LIXI was identified in the SIGN searches but not selected for inclusion as the aim was not to exhaustively review all comparisons within class. DURATION-6 was excluded by AHRQ on the grounds that participants could take non-study drugs for treating diabetes and the results were not stratified by medication. As mentioned above, the recommendation is, in any case, contingent on choice of agent with proven cardiovascular benefit.
	EL	AWARD-1, AWARD-6: Please refer to additional information document	SIGN has included newly published CVOTs released during the lifetime of this guideline, but not other studies which may report comparisons between classes that are already included, or different

			individual drugs within a class which are already described. The GDG has considered the results of these studies and agreed that, given the general policy to not comprehensively review all newly-published non CVOTs, these did not warrant inclusion.
9.1.4	AB	Agreed.	Thank you
	SB	Again, this literature review is incomplete; LEAD 5 compared liraglutide with insulin glargine. Please update. There are also several studies comparing escalation to a full basal-bolus insulin regime (basal plus multiple rapid-acting prandial insulin injections) with basal insulin-GLP-1RA. They show benefits in terms of HbA1c reduction, weight and hypoglycaemia for the basal insulin-GLP-1RA combination; why have they not been included?	This trial was published in 2009, before SIGN 116, and was therefore outwith the search period of this guideline. These further studies do not provide further information on GLP-1 efficacy that is not already included within the guideline.
	JM	Satisfactory.	Thank you
	AZ	Exenatide Once Weekly vs insulin glargine. The DURATION-3 study with Exenatide Once Weekly vs. titrated insulin glargine shows the improvement in HbA1c from baseline was sustained over 3 years. The 156-week results were consistent with those reported in the 26-week interim report. Treatment with once weekly exenatide significantly improved glycaemic control and weight control, compared to the insulin glargine treatment. The safety and tolerability data at 156 weeks were consistent with those reported at 26 weeks. References: *1. Diamant M, Van Gaal L, Stranks S et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label, randomised trial. Lancet 2010; 375: 2234-2243.* *2. Supplement to: Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol 2014* *3. Bydureon SPC*	The original 26 week DURATION-3 trial is included in the AHRQ review, although that document notes that the comparison between metformin + GLP-1 agonist with metformin + basal insulin had insufficient evidence to form a conclusion. SIGN does not refer to it within this section of the guideline. AHRQ excludes the 3 year follow up due to “Background medications; No drug comparison of interest”.
	NovNo	In addition to the trials mentioned in this section we would also like to highlight that there are a few other published trials comparing GLP-1RAs and insulin. In the LEAD-5 trial (liraglutide vs insulin glargine	See above. This trial was published in 2009, before SIGN 116, and was therefore outwith the search window of this guideline.

		and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes (LEAD-5 metformin + sulphonylureas)), liraglutide reduced HbA1c significantly vs insulin glargine (1.33% vs 1.09%; -0.24% treatment difference, 95% CI 0.08 to 0.39; p = 0.0015) and placebo (1.33% vs 0.24%, -1.09% difference, 95% CI 0.90 to 1.28; p < 0.0001). There was greater weight loss with liraglutide vs placebo (treatment difference -1.39 kg, 95% CI 2.10 to 0.69; p=0.0001), and vs insulin glargine (treatment difference -3.43 kg, 95% CI 4.00 to 2.86; p < 0.0001). Rates of hypoglycaemia - major, minor and symptoms only - were 0.06, 1.2 and 1.0 events/patient/year, respectively, in the liraglutide group versus 0, 1.3, 1.8 in the glargine group and 0, 1.0, 0.5 with placebo. (1) *1. LEAD-5, Russell-Jones et al. Diabetologia 2009;52:2046-5* As a comment, we note that reference 70 in the draft guidelines relates to a trial for exenatide versus insulin glargine and not dulaglutide as stated in the second paragraph of 9.1.4.	Thank you. Agreed – typo has been corrected.
	EL	AWARD-2: Please refer to additional information document	AWARD-2 was identified by the SIGN searches but not included. Sufficient evidence comparing GLP-1 agonists with insulin (including dulaglutide with glargine) is already presented in section 8 (revised numbering).
9.1.5	AB	Agreed.	Thank you
	SB	This section is heavily weighted to the only recently licenced combination of lixisenatide and insulin glargine, apparently unaware of a much larger published literature on the fixed ratio of liraglutide and insulin degludec, which has been available in the UK for more than 2 years. Can this either be explained or addressed?	Evidence for the liraglutide/degludec combination is included. We disagree that there is any “heavy weighting” to the lixisenatide and glargine combination. The fixed dose insulin glargine/lixisenatide has a marketing authorisation but not SMC approval. The sentence relating to the combination has been removed.
	JM	Satisfactory.	Thank you
	Sa	Lixisenatide units should be expressed in micro grams. Please amend any deviation from this unit of measurement. Paragraph 2 reads: '(56% v 39%, p<0.0001)'. This should read (28.3% v 12.0%).	Agreed. Units have been corrected. Agreed. Error corrected.

		For references to target HbA1c, please include a measurement (<7%)	Agreed. Value has been added.
	NovNo	The trial comparing the combination therapy of liraglutide/insulin degludec versus insulin degludec alone referenced here is the DUAL II trial, which for reasons outlined below is not an appropriate trial to compare efficacy, weight and hypoglycaemic outcomes between these two therapy options in a clinical setting. DUAL II was a regulatory trial to investigate the contribution of the liraglutide component of liraglutide/insulin degludec versus insulin degludec alone. In order to do this, all trial participants (irrespective of their pre-trial insulin dose) were transferred to a starting dose of 16 units of insulin degludec or 16 dose steps of liraglutide/degludec and up-titrated to a maximum of 50 units of insulin degludec or 50 dose steps of liraglutide/degludec. This piece of information is not mentioned in the guidelines and potentially explains why the hypoglycaemia incidence was comparable between the two groups and why the insulin degludec arm was weight neutral in this particular trial as mentioned under section 9.2. A more clinically relevant trial to consider including would be the Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial (1). This RCT included 557 patients uncontrolled on a basal insulin and metformin who were randomised to either discontinue their pre-trial insulin and start on 16 dose steps of liraglutide/degludec and up-titrate to a maximum of 50 dose steps or to continue with their pre-trial insulin dose as insulin glargine U100 and up-titrate as necessary to achieve control. This trial is more reflective of the treatment options a clinician would have in real life as in the insulin arm the insulin dose is not dropped initially to 16 units and there is no maximum daily insulin dose. Results from DUAL V showed HbA1c level reduction was greater with liraglutide/degludec versus glargine (−1.81% for the liraglutide/degludec group versus −1.13% for the glargine group; (ETD -0.59% (95% CI -0.74% to -0.45%), meeting criteria for non-inferiority (P<0.001), and also meeting criteria for statistical superiority (P<0.001).	Agreed. DUAL II was not designed to investigate glycaemic control and has therefore been removed. The Lingvay study was originally identified in the SIGN evidence table and we note this comment, but do not agree that this adds sufficient new information, as the comparisons are between different insulins.

		Treatment with liraglutide/degludec was also associated with weight loss compared with weight gain with glargine (-1.4 kg for liraglutide/degludec vs 1.8 kg for glargine; ETD, -3.20kg (95% CI -3.77 to -2.64, P<0.001) and fewer confirmed hypoglycaemic episodes (episodes/patient-year exposure, 2.23 for liraglutide/degludec vs 5.05 for glargine; estimated rate ratio, 0.43 (95% CI 0.30 to 0.61, P<0 .001). (1) We therefore suggest that this trial is included in place of DUAL II. *1. Lingway I et al., JAMA. 2016; 315(9): 898-907. doi:10.1001/jama.2016.1252*	
	SMC	Consider whether the final paragraph on insulin glargine/lixisenatide should be amended.	Agreed. This has been removed.
	EL	AWARD-4, AWARD-9: Please refer to additional information document	AWARD-4 is included – see reference 66. AWARD-9 was published in 2017 and is therefore outwith the search period.
9.2	AB	Agreed.	Thank you
	SB	This is an area where clinicians will raise their eyebrows and begin to doubt the validity of NICE and AHRQ reviews, which so dominate this document. GLP-1RAs cause less hypoglycaemia than insulin - period. GLP-1RAs cause more GI upset than other glucose-lowering therapies - period. If this guideline choses to promote alternative truths, based on reviews and meta-analyses, it will lose creditability (and give the impression it has been created by non-clinicians). I would seriously advise a review of this section. When it comes to weight changes, this whole section is confused and confusing. There is much reference to BD exenatide (hardly used now) and albiglutide (not even launched in the UK). There is also confusing reference (72) to the fixed ratio of liraglutide and degludec....	Thank you. We have removed the sentence concerning statistical significance of hypo rates attributed to NICE, however the remaining conclusions are supported by the evidence presented. The majority of evidence is with BD exenatide as first in class. Although it may not be used much, we cannot discount the evidence. Albiglutide is available and has SMC approval. IDegLira has been reworded to show it is a fixed-ratio combination and we will reword this sentence (replace GLP-1 with fixed dose combination) for clarification.
	FG	Worth mentioning that GLP-1 adverse GI symptoms often abate within weeks?	Agreed. This has been added to the Provision of Information section.
	JM	Satisfactory.	Thank you
	NovNo	The statement "The evidence reviewed by NICE indicated that although rates of	Agreed. We have removed the sentence concerning statistical significance of hypo

		hypoglycaemia were numerically lower with GLP-1 therapy compared with insulin, the differences were not statistically significant." is misleading and confusing when later in the document under section 13.1 referring to GLP-1RAs there is the statement: "Hypoglycaemia is much less frequent than with insulin..." The NICE reference states that the overall quality of evidence is low because the network meta-analysis was sparse with many connections limited to a single trial. The NICE guidelines development group also stated that there was no common definition for hypoglycaemia between the trials and that this could have led to bias. Two of the three trials involving GLP-1RAs in the network meta-analysis included sulphonylurea use which is not reflected in the statement and therefore not an adequate reflection of hypoglycaemia rates between GLP-1RAs and insulins. Additionally in all of the RCTs mentioned in section 9.14 (GLP-1RA compared with insulin) all of these showed a significant improvement in hypoglycaemia rates with GLP-1RAs compared to insulin. In our opinion this statement (which only has a level 4 of evidence and based on expert opinion) referring to the NICE review only adds confusion to the guidance and should be removed.	rates attributed to NICE.
		A further trial to consider including, Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active controlled 26-week trial. Body weight was reduced more with liraglutide (3.31kg vs. 1.64kg; ETD: 1.67 kg (95% CI 2.34 to 0.99); p<0.0001). No severe hypoglycaemic episodes were reported and confirmed hypoglycaemia was rare: 3 episodes in 3 patients on sitagliptin (2 were on rescue therapy with either insulin or sulphonylurea) (1) 1. *LIRASWITCH, Bailey TS et al. Diabetes Obes Metab 2016; 18:1191–1198*	Thank you. This was published in December 2016, shortly after SIGN's literature searches were completed. However, the key point (that GLP-1s lower HbA1c more than DPP4 inhibitors) is made clear in the individual evidence summary paragraphs and also the algorithm (which we recognise was not available to the reviewer).
		As mentioned in comments for section 3, the guideline recognises the importance of balancing targets against the detrimental impacts of hypoglycaemia and weight gain; in the same way, and as already included in section 10, we suggest that the added benefits of weight reduction and low risk of hypoglycaemia	We agree that these issues are important and are included in the text, but for consistency and conciseness these are not expressed in the recommendation. They are highlighted in the algorithm.

		gained from GLP-1RAs are reflected in the overall recommendation for GLP-1RA treatment.	
	ABPI	We believe that aspects of this section are confusing and contradictory. The reference statement relating to the NICE meta-analyses and incidence of hypoglycaemia is based on poor quality evidence, including there being no common definition for hypoglycaemia across the trials included or a commonality of included medicines, such that two out of three of the trials included concurrent sulphonylureas which is not reflected in the statement. Additionally, in Section 13.1 of the draft guidelines, it is clearly stated that "Hypoglycaemia is much less frequent [with GLP1 RA's] than with insulin" which is a clear contradiction. We would like to suggest that the statement "The evidence reviewed by NICE indicated that although rates of hypoglycaemia were numerically lower with GLP1 therapy compared with insulin, the differences were not statistically significant" be removed. In this section, it could be helpful to use tables to present complex data.	Agreed. We have removed the sentence concerning statistical significance of hypo rates attributed to NICE.
	EL	AWARD-1, AWARD-2, AWARD-3, AWARD-4, AWARD-5, AWARD-6, AWARD-8, AWARD-9: Please refer to additional information document	AWARD-1 included in SIGN searches, but not selected for inclusion in the guideline. AWARD-2 identified in SIGN searches but not included (see above). AWARD 3-6 included in SIGN evidence table. AWARD 8 and 9 postdated SIGN searches.
9.3	SMC	As you are aware, it has been agreed that all recommendations on medicines issued by Healthcare Improvement Scotland should be aligned. There is a material difference in the draft SIGN recommendation regarding the use of GLP-1 agonists and the current SMC advice for the GLP-1 agonists: the SMC advice restricts these medicines to third-line use which is in line with the Government Diabetes Prescribing Strategy (2014-2016) and the current SIGN Guideline for Diabetes. In particular, the SMC advice for weekly	Agreed. GLP-1 agonists have been recommended as options for third-line therapy in line with SMC advice.

		exenatide (Bydureon; 748/11) states that the economic case for second-line use in combination with metformin in place of a sulphonylurea has not been made and for liraglutide (Victoza; 585/09) the economic case for 2nd line use was not demonstrated (based on a high and uncertain cost-effectiveness ratio). This reflects the economic evidence presented by the company at the time of assessment where the cost effectiveness of these two agents was demonstrated for third line use but not for second line use. Consequently the draft SIGN recommendation is broader than the SMC advice and as such it would permit use of GLP-1 agonists earlier in the treatment pathway where cost effectiveness was not previously demonstrated. We acknowledge that the SMC advice for these medicines was published some time ago and there may be more recent published evidence of cost-effectiveness that SMC has not reviewed. However, if no more recent economic evidence has informed this draft SIGN recommendation, then it would be appropriate to revise the wording of around GLP-1 agonists use to bring it into alignment with SMC advice. SMC would be happy to provide comment on the revisions.	
	SB	In the section on LEADER, there is the suggestion that SU-induced hypoglycaemia may have accounted for the decrease in CV events in those patients assigned Liraglutide. There is no evidence for this in the literature (and there will be data at the ADA in June suggesting that hypoglycaemia did not account for the difference in CV outcomes). But if the guideline-writing group believe this, then they should make a comment in the SU section. In the recommendation, where did the BMI (>30 kg/m^2) suddenly appear from? Why not mention the benefits of GLP-1RA and basal insulin over a full basal-bolus regime in type 2 diabetes? Why is there no mention of the CV benefit of liraglutide (from LEADER) in high CV risk patients?	We have removed this statement as it is not supported by high-quality evidence. The weight criterion was published in SIGN 116 and retained. Further evidence is provided in section 9.1.1 (revised numbering) This will be informed by the algorithm which allows for this combination Thank you. This omission was an error due to the separate chapters being developed by different subgroups and the pressure of time for entering consultation.

		What a missed opportunity, given that so many national guidelines have already taken these points on board....	We have added the following recommendation “In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used”
	FG	I find it an odd argument that a limitation of these studies is the higher rate of hypo in the arm with greater insulin / SU use. Isn’t this just a fact of the treatment options available (i.e. non-GLP options have higher hypo rates) rather than a weakness of the studies? Would an optimal study design have engineered equal amounts of hypoglycaemia between groups?! RECOMMENDATION: I think the recommendation should take into account the likely reduced efficacy in those with longer duration of diabetes (low C-peptide). I also think that GLP-1 analogues should be considered as 3rd line after MF and SGLT2 in people with suboptimal control and established CVD, on the basis of LEADER and SUSTAIN.	We have removed this statement as it is not supported by high quality evidence. The mean duration of diabetes for patients in the LEADER study was 12.8 years. There is little evidence to suggest that longer duration of diabetes reduces efficacy, though clinicians should be aware of the symptoms and signs of insulin deficiency and not delay insulin prescription if required.
	JMc	Semaglutide paper from NEJM as per previous note.	Semaglutide does not have a marketing authorisation and has not been considered by SMC.
	SMac	Agreed.	Thank you
	BK	As above (general comments).	Agreed. We have clarified the recommendation to include a similar statement as for SGLT2 inhibitors “In individuals with type 2 diabetes and established cardiovascular disease, therapy with proven cardiovascular benefit should be used”.
	RCPE	This states that in LEADER ‘a limitation was significantly greater use of insulin and sulphonylureas and a consequent higher rate of hypoglycaemia in the placebo group which may have influenced event rates”. However; it is relevant to mention that in the EMPA-REG nearly double the number of patients in the placebo vs the empagliflozin arm received the addition of insulin (11.5% vs 5.8%) or a sulphonylurea (7% vs 3.8%) with 1.5% of patients in the placebo arm vs 1.3% in the empagliflozin arm experiencing a severe hypoglycaemic event. Therefore the statement referring to the limitation of the	See above. Agreed. We have removed the statement on hypoglycaemia in the placebo group.

		LEADER trial could be removed. Two large international guideline bodies (American Diabetes Association Standards of Medical Care in Diabetes 2017 and Canadian Diabetes Association Clinical Practice Guidelines) have both endorsed liraglutide and empagliflozin in the use with T2D adults with established CVD. GLP1 analogue should be considered as an add-on therapy to metformin in patients with type 2 diabetes when hypoglycaemia is a concern or weight loss is considered to be potentially beneficial. In individuals with type 2 diabetes and established cardiovascular disease, GLP1 RA with proven cardiovascular benefit (currently only liraglutide) in diabetes. SWITCH data now included in the SmPC for degludec yet there is no mention of this.	We have added information about use of agents with cardiovascular benefit to the recommendation. SWITCH 2 was published outwith the search period for this guideline.
	JM	Satisfactory.	Thank you
	Sa	There is a recommendation that GLP-1s should be used in patients with a BMI of 30 kg/m^2 or more. Based on the available evidence for Lixisenatide the benefits are not exclusively for patients with a BMI greater than 30 kg/m^2. In Reference 74, the mean ± SD BMI at baseline was 32.1 ± 6.2, with 40% of patients having BMI < 30 and 60% of patients having BMI ≥ 30. In Reference 75, the mean ± SD BMI at baseline was 31.8 ± 6.3, with 46.2% of patients having BMI < 30 and 53.8% of patients having BMI ≥ 30.	This statement has been carried over from SIGN 116. Given the mean BMI of patients recruited to these studies, the GDG has agreed to retain the existing published weight criteria for GLP-1 agonists.
	AB	I believe your recommendation needs some further consideration. I agree with the first two-thirds of your recommendation but why do you recommend GLP-1 RAs as an alternative to insulin treatment in patients where treatment with metformin or sulphonylurea (or both) at MAXIMALLY tolerated doses has been inadequate. Firstly, there is no dose response for metformin beyond 1000mg twice daily (so why push people to increase it with massively increased risk of gastrointestinal side-effects) or increase	Agreed. We have clarified this recommendation by removing the final phrase.

		sulphonylurea dose (very little improvement in glycaemia when using more than half the recommended maximum dose but increased risk of side-effects). In addition, why not also be able to use GLP-1 RAs in people failing on other oral agents? Why specify sulphonlyureas, for example, to the exclusion of other drugs? Also, given we have a major CV outcomes trial (LEADER) showing CV benefit and reduced CV mortality in high-risk patients why is this not part of your recommendation?	
	MF	Recommendation for GLP-1 RAs is rather unwieldy and could be split into two. There should also be a third rec, similar to that for SGLT2 inhibitors, recommending use on proven GLP-1 RAs in individuals with existing cardiovascular disease.	Agreed. We have reworded the original recommendation and split into three statements.
	NP	The recommendations made in this section compared with Section 10.3 seem imbalanced in favour of promoting the use of the SGLT2 inhibitor, Empagliflozin for providing "proven cardiovascular benefit" with no such benefit recognised in the recommendation for the GLP-1 RA, liraglutide. Specific relevant points include: -	Noted. We have added information about cardiovascular benefit to the GLP-1 recommendation.
		1. The HRs for empagliflozin and liraglutide in relation to the same standard 3-point cardiovascular MACE was 0.86 (p=0.04 for superiority) and 0.87 (p=0.01 for superiority) respectively. Both agents were associated with significant reductions in cardiovascular death and all cause death.	CV benefit has been added.
		2. Both agents reduced hospitalisations for heart failure but only significantly so for empagliflozin.	Noted.
		3. However, (not mentioned in Section 10.3) empagliflozin was associated with an 18% and 24% increase in fatal and non-fatal stroke respectively (albeit not statistically significant). This compared with a non-significant reduction of 14% and 11% in fatal and non-fatal stroke associated with liraglutide use.	Thank you. These non-significant effects are treated equally in the SGLT2 and GLP-1 sections, ie not reported.
		4. Liraglutide reduced nephropathy rate compared with placebo by 22% (p=0.003). This was not mentioned in Section 9.3 but the renal benefits of empagliflozin were included in section 10.3.	We have added a sentence to reflect this point.
		5. The first sentence of the first paragraph	Disagree. This statement is already

		of section 10.3 should have appeared in section 9.3 also, since it is common and generic to both classes.	included in section 1.1 and will be removed from later sections.
		6. The cardiovascular benefits of liraglutide observed in LEADER are potentially explained in section 9.3 by increased use of insulin and sulphonylureas. That may be true but it is conjectural and does not detract from the observed cardiovascular benefits whilst causing no cardiovascular harm.	Agreed. We have removed this sentence.
		7. The disparity in recommending the SGLT2i empagliflozin but not liraglutide for cardiovascular reduction is not compatible when with the facts or with the ADA Standards of Medical Care in Diabetes or with the Canadian Diabetic Association Clinical Practice Guidelines.	Agreed – we have added CV benefit to the recommendation.
		8. The apparently different mechanisms of action and hence likely cardiovascular benefits produced by the SGLT2i empagliflozin and GLP1RA, liraglutide mean they provide potentially different patient targets for preventing cardiovascular events and to only recommend one agent and not the other seems biased, ill-considered and clinically unsound.	Noted. All agents with proven cardiovascular benefit have now been highlighted in the respective recommendations.
	AZ	EXSCEL (Exenatide [once-weekly Bydureon] Study of Cardiovascular Event Lowering) trial randomized 14,752 patients, including those with and without cardiovascular risk and prior history of CV events. Overall, 73% of randomized patients (N=10,781) had experienced at least one prior CV event, while 27% (N=3,969) of randomized patients had not experienced any prior CV event. EXSCEL trial met its primary safety objective, showing that once-weekly Bydureon did not increase cardiovascular (CV) risk in a broad population of patients with type-2 diabetes (T2D) who have a wide range of CV risk. In addition, the top-line results showed fewer events were observed in the patients treated with Bydureon, however, the primary efficacy objective did not reach statistical significance. The full results being presented at the European Association for the Study of Diabetes (EASD) meeting in September 2017.	Thank you. At the time of consultation this was from a press release only, which is not a form of evidence eligible for use in SIGN guidelines. As a result of the CVOT publishing during the lifetime of the guideline, this has now been reviewed and incorporated.

		Reference: *Press release (Published 23rd of May 2017), available from https://www.astrazeneca.com/content/astraz/media-centre/press- eleases/2017/bydureon-exscel-trialmeets-primary-safety-objective-in-type-2-diabetes-patients-at-wide-range-of-cardiovascular-risk-23052017.html* Recommendations (Chapter 9): AstraZeneca suggests applying consistency (with SGLT2-inhibitor recommendations section) in the guidance document by adding a recommendation that ensures the guidance is future proof: 'GLP1 receptor agonists with proven cardiovascular benefits or cardiovascular safety are recommended to be used in eligible patients in respective trial identified patient populations'.	Agreed. We have included a new recommendation which specifies 'proven CV benefit' as a criterion.
	NovNo	Novo Nordisk believes that the inclusion and interpretation of evidence relating to GLP-1RAs and the consequent recommendation does not adequately reflect the body of evidence and the clinical benefits of GLP-1RA therapy. In particular, the latest evidence from the cardiovascular outcome trial, LEADER, has not been sufficiently acknowledged to allow a clear recommendation, unlike the wording in Section 10.3 relating to SGLT2 inhibitors. The rationale of such a conclusion is unclear to us and is unaligned with other clinical guidelines across Europe and North America (detailed below). The mechanisms of action of these two classes of medicines are very different both in terms of glycaemic control and also their potential mechanism on cardiovascular events therefore we believe it is crucial to provide the full evidence and recommended options to enable clinicians to choose the most suitable treatment for adults with type 2 diabetes at high risk of cardiovascular disease. The LEADER trial demonstrated a significant reduction of the primary composite outcome of major cardiovascular events by 13% (HR 0.87; 95% CI 0.78 to 0.97; p<0.001 for non-inferiority; p=0.01 for superiority), and a significant reduction of cardiovascular death by 22% (HR 0.78; 95% CI 0.66 to 0.93; p=0.007). (1)	The recommendation has been split into separate smaller statements for clarity and we have added information about use of agents with cardiovascular benefit.

		Additionally we would like to highlight that LEADER also showed a significant 22% (HR 0.78, 95% CI 0.77 to 0.92); p=0.003) reduction with liraglutide in the composite renal outcome comprising the number of patients developing persistent macroalbuminuria, doubling of serum creatinine, the need for continuous renal replacement therapy or death due to renal insufficiency. Section 9.3 of the document states regarding the LEADER trial that 'a limitation was significantly greater use of insulin and sulphonylureas and consequent higher rate of hypoglycaemia in the placebo group which may have influenced event rates.' We would like to make you aware that a post hoc analysis, due to be presented at ADA 2017 and still under embargo, examined the potential associations between severe hypoglycaemia and time to first Major Adverse Cardiac Event (MACE), CV death and all-cause death. In this analysis, patients with or without severe hypoglycaemia were compared and adjusted for different periods of follow-up with their randomised treatment. The protective effect of liraglutide on risk of MACE was unchanged when patients with severe hypoglycaemia were excluded from the analysis. Moreover patients with severe hypoglycaemia only accounted for 5% of all MACE in the trial. Additional analysis (also due to be presented at the ADA and currently under embargo) showed when patients who were started on SU/TZD during the trial were censored from the analyses, the MACE remained significant (HR 0.83, 95% CI 0.70 to 0.98). (2) We therefore feel the statement referring to the limitation of the LEADER trial should be removed. We would also like to bring to your attention that the evidence from the LEADER trial has been submitted for inclusion in the Summary of Product Characteristics (SmPC) for liraglutide and is currently under review with a potential update by the end of the 2017. Recent updates from large international guideline bodies currently recommend empagliflozin and liraglutide for patients with Type 2 diabetes and established cardiovascular disease: i) American Diabetes Association Standards of Medical Care in Diabetes 2017 – "Based on the results of two large clinical trials, a recommendation was	

		added to consider empagliflozin or liraglutide in patients with established cardiovascular disease to reduce the risk of mortality." ii) Canadian Diabetes Association Clinical Practice Guidelines – "In adults with type 2 diabetes with clinical cardiovascular disease in whom glycaemic targets are not met, an anti-hyperglycaemic agent with demonstrated cardiovascular outcome benefit should be added to reduce the risk of major cardiovascular events (Grade 1, Level 1A for empagliflozin (2); Grade 1, Level 1A for liraglutide if age ≥50 years (3); Grade D, Consensus for liraglutide if age <50 years)." iii) Italian Association of Clinical Diabetologists – "EMPA REG and LEADER fully justify an additional indication that includes specifically those T2D patients with pre-existing CVD (present in about 20% of patients with T2D)" iv) Swiss Society for Endocrinology and Diabetes treatment guidelines – "So far, only empagliflozin and liraglutide could demonstrate a reduction of mortality. In the presence of CVD, empagliflozin and liraglutide are preferred. A class effect cannot be assumed, recommendations apply only for empagliflozin and liraglutide. Taking the above points into consideration we therefore suggest that section 9.3 should be aligned with section 10.3 as follows: "GLP-1RAs should be considered as an add-on therapy to metformin in patients with type 2 diabetes when hypoglycaemia is a concern or weight loss is considered to be potentially beneficial. In individuals with type 2 diabetes and established cardiovascular disease, GLP-1 RAs with proven cardiovascular benefit (currently only liraglutide) in diabetes are appropriate agents to add in with metformin" References: *1. LEADER, Marso et al. New Engl J Med 2016;375:311–22* *2. Poster #359OR due to be presented at ADA 2017 and still under embargo — 2017 ADA 77th scientific session. Severe Hypoglycemia, Cardiovascular Outcomes, and Death – The LEADER Experience. Bernard Zinman, Steven P Marso, Erik*	

		Christiansen, Salvatore Calanna, Soren Rasmussen, John B Buse	
	NHSLot	Section 10.3 on SGLT2 inhibitors does mention a reduction in a composite renal outcome in the EMPA-REG trial (empagliflozin). In the interests of fairness, the reduction in nephropathy observed in the LEADER trial should therefore be mentioned in section 9.3. It is also pertinent to note that section 10.3 explicitly (and appropriately) singles out empagliflozin as being the only SGLT2 inhibitor with cardiovascular benefit and it might be argued that a similar wording should be used for the GLP-1 recommendation following section 9.3.	The recommendation has been split into separate smaller statements for clarity and we have added information about use of agents with cardiovascular benefit. We have added a sentence to reflect the nephropathy outcome.
Section 10			
General	RCPL	Info on gliflozins and active for problems.	No specific point has been made.
	AG	Newest 'kids on the block' and, I suspect, a major reason for the update. The information provided in the guideline gives a good account of those SGLT2 studies undertaken to date, emphasising where the therapies fit in in terms of positioning and highlighting exciting cardiovascular data.	Thank you. Noted
	AB	I agree with your recommendations BUT strongly advise that you delay the final iteration until the CANVAS trial results with canagliflozin are announced at the American Diabetes Association in early June 2017 (this will also coincide with the major publication). If SGLT2 inhibitors have CV benefits as a class this is extremely important and should be included in this Guideline. The results will be available well before publication so it seems ludicrous not to include this in supporting/changing your recommendations ie whether you will recommend a single drug or the whole drug class in this context.	Agreed. While SIGN will not be carrying out further literature searches, high-profile ongoing CVOTs which publish during the period from consultation to a cut off prior to publication have been reviewed and, if appropriate, incorporated.
	MF	The first rec for SGLT2 inhibitors is fine. The second should be amended as it is illogical to specifically mention in combination with metformin for CVD benefits. Although metformin was the commonest single baseline treatment nearly half of the patients in EMPA-REG OUTCOME were on insulin at baseline. There has not been any published analysis of differences in response based on baseline therapies.	Noted. The intention was to place empagliflozin as a second-line agent with metformin remaining first line as per SIGN 116, but we agree for the study population used empagliflozin was added on to other baseline therapies including insulin. The algorithm will position it after metformin and this recommendation has been revised.

	BK	Very good summary of the recent evidence and a directed recommendations for those with established CV disease is welcome.	Thank you. Noted
	RCP	Well-presented section.	Thank you. Noted
	RCPE	We are unsure why there is so much on SGLT2i as monotherapy as the Scottish Medicines Consortium (SMC) has not approved any SGLT2i for monotherapy.	The review of the evidence was to ascertain clinical benefit including evidence for efficacy and safety. SMC has accepted SGLT2 inhibitors for use in patients who are unable to tolerate metformin as monotherapy.
		Tables presented are as monotherapy and could direct people to an area that SIGN is not recommending usage. Text appears to present NICE meta–analysis. The evidence review group within NICE were clear that there were uncertainties with the analysis and it should be treat with caution.	Noted. The tables have been removed and noted to be consistent with the individual trial results presented.
		Monotherapy not recommended by SMC or within SIGN – more emphasis should be placed in reviewing data from SMC approvals for the Add onto Met SIGN recommendation.	See above
		It would be better to use Detailed Advice Document from SMC (as below). Baseline 24/26 week Dapa 10 7.92% 0.84% Cana SU 100 7-7.9% 0.82% Cana SU 300 0.93% Cana D 100 7-10% 0.79% Cana D 300 0.94%	Noted. The tables have been removed and noted to be consistent with the individual trial results presented.
		With SGL2i there is no comment on fractures/amputations.	Canagliflozin has been associated with increased risk of fractures and reduced bone mineral density. There is no conclusive evidence of similar effects with dapagliflozin or empagliflozin at this time. Canagliflozin has also been associated with an increased risk of lower limb amputations. The text has been updated accordingly to reflect these points.
	ME	The inclusion of the EMPA REG data is entirely appropriate, in addition differential glucose lowering efficacy data for the three different agents within class should be considered. Canagliflozin 300 mg OD may be considered as having greater glucose lowering efficacy and since these agents are glucose lowering drugs this issue should be considered within the	Thank you for this comment. There are no head to head trials for different SGLT2s. It would be inappropriate to use indirect comparisons to suggest one drug at a particular dose is more efficacious and clinically relevant.

		guideline as this has potential budget impact and cost effectiveness implications.	
	JM	Satisfactory. It is good to see this section included.	Thank you. Noted
	Ta	The amount of information included in the glycaemic control section for the SGLT2 inhibitor class is much greater than that for the other classes, for example for the SGLT2 inhibitors, the glycaemic control section is split into two sections - monotherapy (10.1.1) and combination therapy (10.1.2), which is not the case for other agents (e.g. thiazolidinediones, DPP-4 inhibitors, both with only a single section on glycaemic control). Whilst we agree the content is sound, the increased level of focus on this class of therapy may have the inadvertent effect of differentially highlighting and therefore encouraging greater prescribing of SGLT2 inhibitors vs. other agents. We suggest the depth of information provided in this section for efficacy vs. other classes is consistent with that provided for other agents increased so the content is balanced.	The length of the sections is dictated by the amount of evidence identified in the literature searches rather than an intention to highlight one class over another. However two tables have been removed.
	DS	Indicate SGLT2 as an option for monotherapy when other therapies such as Metformin, Sulphonylurea, etc. are contraindicated or tolerated.	We presume this is meant to read 'not tolerated'. The class is licensed for monotherapy. We have included a paragraph summarising the approval of SGLT2 as monotherapy in restricted circumstances. A number of second-line agents are approved for use in patients intolerant of metformin, therefore, for conciseness we have not shown these in the algorithm.
10.1.1	AG	See above	Thank you. Noted
	AB	Agreed.	Thank you. Noted
	ABI/EL	We have noticed that unlike the other diabetes drugs classes, SGLT2i was the only class that includes Network Meta-Analysis table comparing the effect of SGLT2i of HbA1c. Whereas for each of the other diabetes drug classes which you discuss in the guidelines, the data is all in prose/text format, rather than in tables. Therefore, for consistency, we are suggesting to remove this NMA table. In addition,as there is no head-to-head trial comparing these SGLT2i directly, it is not advisable to use NMA to compare between drugs in a clinicalguideline setting taking in consideration the effect	See above – the tables have been removed.

		of differences in study design, protocol, patients characteristics etc. on the results.	
	JM	Satisfactory.	Thank you. Noted
	AZ	The monotherapy section currently appears emphasised which is inconsistent with the remainder of the document. The emphasis is particularly concerning considering that of patients in the UK prescribed a SGLT2-inhibitor, 3% are prescribed an SGLT2-inhibitor as monotherapy, with 97% prescribed a SGLT2-inhibitor in combination with other therapies (reference 1).	This section is now shorter following removal of the table.
		Following NICE Multiple Technology Appraisal (MTA) Guidance (TA 390) (reference 2) – canagliflozin, dapagliflozin and empagliflozin are now recommended as options for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if: a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.	This has been added to the guideline.
		The text in the draft guidance does not fully reflect the full nature of the meta-analysis conducted, and does not note the key issues when interpreting the analysis as highlighted by the NICE assessment group (TA390 section 3.23). Furthermore, there was high heterogeneity between studies which means that the difference in results may not be only because of the drug, but also influenced by differences in trial design and patient baseline characteristics.	
		The SIGN guidelines rightly highlight that the baseline HbA1C for a canagliflozin trial was 8%; but do not note that conversely, dapagliflozin had a trial with a baseline HbA1c of 7.5%; thus, the magnitude of difference versus placebo between these trials is expected to be different.	Agreed. The baseline HbA1c for the dapagliflozin and empagliflozin trials have been added.
		In a sensitivity analysis conducted by AstraZeneca during the NICE MTA, removing Kaku et al, showed that the results for dapagliflozin lowering HbA1c	The tables containing these data have now been removed.

		versus placebo changed from -0.62 (-0.89, -0.35), to -0.75 (-1.08, -0.43). AstraZeneca recommends that the SIGN guidelines clarify the limited evidence base, differences in baseline characteristics, and limitations of interpreting the meta-analyses as highlighted by NICE. Please note that based on the evidence available, NICE did not recommend one SGLT2-inhibitor over the others. We also recommend that the tables 2 (10.1.1) and 3 (10.2) are removed for consistency with the remainder of the document. References *1. Patient Data, IMS Health Ltd, MAT March 2017 - please note that the calculation is based on the most commonly prescribed SGLT2 combinations* *2. NICE adult type 2 diabetes in adults: Guidance, available from https://www.nice.org.uk/guidance/ta390/resources/canagliflozin-apagliflozin-and-empagliflozin-asmonotherapies-for-treating-type-2-diabetes-pdf-82602903454405* AstraZeneca also suggests to add in a third recommendation for SGLT2-inhibitors to be used in monotherapy in line with NICE Multiple Technology Appraisal (TA 390) advice.	The tables containing these data have now been removed. Noted Agreed. The tables containing these data have now been removed. Disagree. The guideline does not list all possible indications, though the possible use of SGLT2 inhibitors as monotherapy under restricted circumstances has been noted in the algorithm.
10.1.2	AG	See above	Thank you. Noted
	AB	Agreed.	Thank you. Noted
	ABI/EL	To have a consistent, fair and balanced presentation of the available trials, we are suggesting to include the information about empagliflozin's insulin trials, particularly as the reader may get the impression that such trials do not exist and thus such combination is not recommended. There are two insulin trials with empagliflozin – one is with basal insulin, the other is with MDI (multiple daily injections) the references for these trials are as follows : 1. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycaemia with empagliflozin added to titrated multiple daily injections of insulin in	The trials referenced in this comment were not included as they did not fit the inclusion criteria (n<200 per group) used to select papers from the literature search. We have described the exclusion criteria more explicitly in section 14.1. We have cited four studies demonstrating the addition of SGLT2 inhibitors to patients already on insulin. No further action required.

		obese inadequately controlled type 2 diabetes *Rosenstock et al, Diabetes Care, 2014, 18151823.* 2. Basal insulin: Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78- week randomized, doubleblind, placebo-controlled trial. *Rosenstock et al, Diabetes, Obesity and Metabolism, 2015, 17, 936-948.*	
	NG	Comment on SGLT2 with GLP-1 and/or insulin with commenting on, even if no/little evidence - http://www.practicaldiabetes.com/article/addition-sglt2-inhibitor-glp-1-agonist-therapy-people-type-2-diabetes-suboptimal-glycaemiccontrol/	This study was a retrospective case note review, n=14 examining SGLT2 when added to GLP-1 agonists in patients with suboptimal glycaemic control and was therefore not selected for review.
	JM	Satisfactory.	Thank you. Noted
	Sa	The recommendations made in this section compared with Section 9.3 seem imbalanced in favour of promoting the use of the SGLT2 inhibitor, Empagliflozin for providing "proven cardiovascular benefit" with no such benefit recognised in the recommendation for the GLP-1 RA, liraglutide. Specific relevant points include: - 1. The HRs for empagliflozin and liraglutide in relation to the same standard 3-point cardiovascular MACE was 0.86 (p=0.04 for superiority) and 0.87 (p=0.01 for superiority) respectively. Both agents were associated with significant reductions in cardiovascular death and all cause death. 2. Both agents reduced hospitalisations for heart failure but only significantly so for empagliflozin. 3. However, (not mentioned in Section 10.3) empagliflozin was associated with an 18% and 24% increase in fatal and non-fatal stroke respectively (albeit not statistically significant). This compared with a non-significant reduction of 14% and 11% in fatal and non-fatal stroke associated with liraglutide use. 4. Liraglutide reduced nephropathy rate compared with placebo by 22% (p=0.003). This was not mentioned in Section 9.3 but the renal benefits of empagliflozin were included in section 10.3. 5. The first sentence of the first paragraph	Thank you. Inconsistency in the wording of CV effects in the recommendations for SGLT2 inhibitors but not GLP-1 agonists in the draft was an error due to the separate chapters being developed by different subgroups and the pressure of time for entering consultation; this has been corrected. The empagliflozin effect becomes apparent earlier and this and other features mean that their benefits can be taken to be similar. See previous response

		of section 10.3 should have appeared in section 9.3 also, since it is common and generic to both classes. 6. The cardiovascular benefits of liraglutide observed in LEADER are potentially explained in section 9.3 by increased use of insulin and sulphonylureas. That may be true but it is conjectural and does not detract from the observed cardiovascular benefits whilst causing no cardiovascular harm. 7. The disparity in recommending the SGLT2i empagliflozin but not liraglutide for cardiovascular reduction is not compatible when with the facts or with the ADA Standards of Medical Care in Diabetes or with the Canadian Diabetic Association Clinical Practice Guidelines. 8. The apparently different mechanisms of action and hence likely cardiovascular benefits produced by the SGLT2i empagliflozin and GLP1RA, liraglutide mean they provide potentially different patient targets for preventing cardiovascular events and to only recommend one agent and not the other seems biased, ill-considered and clinically unsound.	
	AZ	Please note that dapagliflozin 2.5 mg is not available in the UK hence we therefore suggest related data are removed from the draft guidance document. All three SGLT2 inhibitors are recommended in this position. We propose that dapagliflozin and canagliflozin evidence are referred to for completeness/balance. For dapagliflozin please refer to: *1. Jabbour et al Diabetes Care 37 March 2014. Dapagliflozin is effective as Add-on Therapy to Sitagliptin With or Without Metformin: A 24-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study* Baseline HbA1c and FPG levels were 7.9% (63.0 mmol/mol) and 162.2 mg/dL (9.0mmol/L) for the dapagliflozin group and 8.0% (64.0mmol/mol) and 163 mg/dL (9.0 mmol/L) for placebo. At week 24, dapagliflozin significantly reduced mean HbA1c levels (–0.5% [–4.9 mmol/mol]) versus placebo (0.0% [+0.4 mmol/mol]). Dapagliflozin reduced body weight versus placebo (–2.1 and –0.3 kg),	Thank you for your comment. Whilst the 2.5 mg dose of dapagliflozin is not available in the UK if studies are used including this dose then the results are reported for completeness. This paper has been reviewed and incorporated.

		2. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. This RCT aimed to compare the efficacy and safety of co-initiation of the GLP-1 once weekly receptor agonist exenatide and the SGLT2 inhibitor dapagliflozin with once weekly exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled by metformin. After 28 weeks, the change in baseline HbA1c was −2·0% (95% CI −2·1 to −1·8) in the exenatide plus dapagliflozin group, −1·6% (−1·8 to −1·4) in the exenatide group, and −1·4% (−1·6 to −1·2) in the dapagliflozin group. Exenatide plus dapagliflozin significantly reduced HbA1c from baseline to week 28 compared with exenatide alone (−0·4% [95% CI −0·6 to −0·1]; p=0·004) or dapagliflozin alone (−0·6% [–0·8 to −0·3]; p<0·001). Exenatide plus dapagliflozin was significantly superior to either drug alone for all secondary efficacy endpoints, with greater reductions in fasting plasma and postprandial glucose, more patients with an HbA1c less than 7·0% (<53 mmol/mol), greater weight loss, a greater proportion of patients with weight loss of 5% or more, and greater reductions in systolic blood pressure (all p≤0·025). Reference *2. Juan P Frias et al (published 16 Sept 2016), available from: http://www.thelancet.com/journals/lancia/article/PIIS2213-8587(16)30267-/fulltext* For information, we include the efficacy and weight change in one of the most commonly used SGLT2- inhibitor combinations (metformin +sulphonylurea +SGLT2- inhibitor). In this combination, the trials indicate a similar efficacy across the class. SGLT2 inhibitors - in combination therapy with metformin and sulphonylurea In brackets (primary endpoint HbA1c change from baseline, secondary endpoint change from baseline, study length): Canagliflozin 300mg (-1.06%, -2.60kg, 26	The DURATION 8 study was published outwith the search period for this guideline and, as not a CVOT, is not being specifically reviewed.

		weeks) Dapagliflozin 10mg (-0.86%, -2.65kg, 24 weeks) Canagliflozin 100mg (-0.85%, -2.10kg, 26 weeks) Empagliflozin 10mg (-0.82%, -2.16kg, 24 weeks) Empagliflozin 25mg (-0.77%, -2.39kg, 24 weeks) References: *Dapagliflozin (SPC) https://www.medicines.org.uk/emc/medicine/27188* *Canagliflozin (SPC) https://www.medicines.org.uk/emc/medicine/28400* *Empagliflozin (SPC) https://www.medicines.org.uk/emc/medicine/28973*	
	JN	"SGLT2 inhibitors should be considered as an add-on therapy to metformin in patients with type 2 diabetes when hypoglycaemia is a concern or weight loss is considered to be potentially beneficial." Janssen and Napp request that additional information be added here to reflect the licence use of canagliflozin as well as the NICE guidelines which recommend use as dual and triple therapy. Suggest the following wording be considered 'SGLT2 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c in combination with metformin, sulphonylureas, thiazolidinedione's, DPP4 inhibitors or insulin' Reference: •*Canagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28400 (last accessed 22/05/2017)* 4.1 Therapeutic indications Invokana is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as: • Monotherapy When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications. • Add-on therapy Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate	We have amended the recommendation and removed the reference to first-line therapy options.

		glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies). *NICE algorithm update May 2017 https://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood- glucose-lowering-therapy-in-adults-with-type-2-diabetes-pdf-2185604173*	
10.2	AG	See above	Thank you
	AB	Agreed.	Thank you
	ABI/EL	DDP should be DPP.	Thank you for your comment. This typo has been corrected.
	SB	P24. 10.2. There is no mention of the side-effects of bone mineral density loss (canagliflozin) or amputation (canagliflozin) which are now included in the SPC.	Thank you for your comment. Canagliflozin has been associated with an increased risk of amputation and fractures and the text has been updated accordingly.
	FG	Low endogenous insulin secretion – how is this defined or assessed?	Thank you for your comment. This refers to information given by EMA/MHRA which is referenced in the guideline. This defines a risk factor for DKA as "patients with low beta cell reserve eg, patients with type 2 diabetes who have low C-peptide levels, latent autoimmune diabetes in adults [LADA], or a history of pancreatitis." See also www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis
	SMac	FDA have added boxed warning to Canagliflozin for increased amputation risk recently, apologises re no information on evidence.	Noted. We have added further comment on amputation risk linked to the CANVAS study.
	NovNo	It is important to highlight that on 24 February 2017, the European Medicines Agency (EMA) flagged a potential increased risk of lower limb amputation (mostly affecting the toes) in patients taking the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes.(1) *1.http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/02/news_detail_002699.jsp&mid=WC0b01ac058004d5c1*	See above
	JMc	Satisfactory. I accept that DKA is an adverse effect and I suppose that the last paragraph is situated appropriately.	Thank you
	AZ	We recommend that the table 3 is removed for consistency with the remainder of the document. Please see additional information in 13.1	This table has been removed.

		under SGLT2-Inhibitors.	
	JN	No comment within the guidelines regarding the effect of SGLT2 inhibitors on blood pressure Canagliflozin (and other SGLT2 inhibitors), although not licensed for blood pressure control, have a lowering effect on systolic blood pressure. Janssen and Napp request that this effect is acknowledged within the guidelines as well as a recommendation of caution as detailed in the reference section below. Reference: *Canagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28400 (last accessed 22/05/2017)* 4.4 Special warning and precautions; Use in patients at risk for adverse reactions related to volume depletion Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an eGFR < 60 mL/min/1.73 m2, patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age) 5.1 Pharmacodynamic properties; Mechanism of action The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes. Blood pressure In placebo-controlled studies, treatment with canagliflozin 100 mg and 300 mg resulted in mean reductions in systolic blood pressure of -3.9 mmHg and -5.3 mmHg, respectively, compared to placebo (-0.1 mmHg) and a smaller effect on diastolic blood pressure with mean changes for canagliflozin 100 mg and 300 mg of -2.1 mmHg and -2.5 mmHg, respectively, compared to placebo (-0.3 mmHg). There was no notable change in heart rate.	Thank you for these detailed comments BP was not an outcome in the key questions; text regarding effects on blood pressure was therefore removed in the circulated draft.

10.3	AG	See above	Thank you
	AB	Agreed.	Thank you
	ABI/EL	In the 4th paragraph, please consider adding the word 'significant' before reduction in the renal paragraph (as empagliflozin resulted in a statistically significant reduction in composite renal outcomes in the EMPA REG Outcome trial).	Agreed. The text has been revised.
	SB	The recommendation for empagliflozin use in patients with type 2 diabetes (EMPA-REG 14% reduction in the primary MACE endpoint) and high CV risk only goes to highlight the lack of such a recommendation for liraglutide (LEADER 13% reduction in primary MACE endpoint). There needs to be some consistency....	Thank you. Inconsistency in the wording of CV effects in the recommendations for SGLT2is but not GLP-1s in the draft was an error due to the separate chapters being developed by different subgroups and the pressure of time for entering consultation; this has been corrected.
	FG	Probably important to emphasise that event reduction in EMPA-REG was driven by secondary prevention. Should there be a clearer message here that empagliflozin SHOULD BE the 2nd line agent in those with established CVD? The R statement is fairly bland 'hypo a concern or weight loss beneficial' isn't that almost everyone?	Agreed. The text has been revised to show baseline proportions with CVD. Recommendation has been clarified with empagliflozin and canagliflozin recommended as alternatives – the metformin comment has been removed.
	JM	I am not 100% convinced that the second recommendation here flows from the preceding material. In the trial cited, it compared empagliflozin with placebo and there does not appear to be any mention of metformin. Perhaps some of this needs to be reviewed?	See above.
	AZ	AstraZeneca would like to make the committee aware of additional cardiovascular data for the SGLT2 inhibitors: 1. The cardiovascular (CV) safety of dapagliflozin has been demonstrated in a meta-analysis of 21 Phase IIb/III trials from the clinical development programme. This population consisted of 9,339 patients (10,550 patient years of exposure) with a broad degree of CV risk, including 3,214 patients with a history of CV disease. A total of 176 major adverse cardiovascular endpoints (MACE) plus unstable angina (UA) events were observed in the overall population; 95 events in patients receiving dapagliflozin and 81 events in patients receiving control [HR 0.79; 95 % CI (0.579, 1.070)]	Supplemental searches carried out by SIGN to update the existing meta-analyses were limited to RCTs only. This is a meta-analysis of RCTs and therefore not identified. It appears to show cardiovascular non-inferiority compared with placebo/control.

		(reference 1) 2. Lower Risk of Heart Failure and Death in Patients Initiated on SGLT2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (references 2,3,4) Data were collected via medical claims, primary care/hospital records and national registries from the US, Norway, Denmark, Sweden, Germany and the UK. Propensity score for SGLT2i initiation was used to match treatment groups. Hazard ratios (HRs) for HHF, death and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany. The CV outcomes of the SGLT2 inhibitor class including dapagliflozin were further investigated in the CVD-REAL study. CVD-REAL is a retrospective observational outcomes study comprising healthcare records from over 300,000 patients with type 2 diabetes from across six countries. The study assessed the endpoints of hospitalisation for heart failure (hHF) and all cause death (ACD) in new users of an SGLT2 inhibitor compared to new users of other glucose lowering medications (oGLD). New users of an SGLT2 inhibitor (n=154,523) were first propensity matched 1:1 across multiple variables to new users of oGLDs, ensuring well matched characteristics and risk profiles at baseline. This study demonstrated that new users of an SGLT2 inhibitor were associated with a 39% and 51% relative risk reduction (RRR) in the endpoints of hHF and ACD respectively versus oGLDs. The SGLT2 inhibitor population consisted of approximately 47% dapagliflozin, 47% canagliflozin and 5% Empagliflozin treated patients (reference 2). In a further sub-study of patients from the Norwegian and Swedish national registry data bases, new users of dapagliflozin (n=8,582) were propensity matched 1:3 with new users of a DPP-4 inhibitor (n=25,746) (reference 3). Patients who were newly initiated on dapagliflozin were associated with a 29% and 27% RRR in MACE and ACD endpoints respectively, compared to those initiated on the DPP4 inhibitor class. Together these data suggest that the effect on CV outcomes observed in	Reference 2 was published in May 2017, therefore not identified by the SIGN literature searches. Reference 3 is a poster, therefore not eligible for use in the SIGN guideline. Reference 4 is EMPA-REG which is already included in the guideline.

		the EMPA-REG OUTCOME trial (reference 4) may be a class effect and may also translate to a population without established cardiovascular disease. 3. The CV profile of dapagliflozin will be further elucidated in the ongoing DECLARE study as noted by the committee. DECLARE has enrolled 17,000 patients, including a high proportion of patients without established CV disease and is due to report in 2019 (reference 5) References: *1. Sonesson C et al. Cardiovasc Diabetol. 2016;15:37* *2. Kosiborod et al.; CVD-REAL Study (published 18th of May 2017) Available from: http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190* *3. Norhammar A, et al. Poster (P3008) presented at European Society of Cardiology - Heart Failure meeting; April 29 – May 2, 2017; Paris, France.* *4. Zinman B, et al. N Engl J Med. 2015 0028-4793* *5. http://www.timi.org/index.php?page=declare-timi-58* AstraZeneca recommends ensuring the guidelines are future proofed prior to the next update as new evidence emerges and marketing authorisations are updated, by changing the second recommendation to: 'SGLT2 inhibitors with proven cardiovascular benefits or cardiovascular safety are recommended to be used in eligible patients in respective trial identified patient populations'	Reference 5 is ongoing as noted in the guideline. CVOTs has been used to support recommendations on cardiovascular benefit and safety in this guideline. We have highlighted the ongoing DECLARE-TIMI study. Noted. No change required. Future reviews will consider the available evidence at the time of update.
	NHSsig	Important to specify that EMPA REG population were very high risk patients with known cardiovascular disease. It would be helpful to note that the primary end point in EMPA REG was driven by the reduction in CV death that Stroke & MI were not reduced (stroke was marginally increased although not significantly)	Agreed. This has been emphasised. Noted.
	JN	"In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibition and proven cardiovascular benefit (currently only empagliflozin) are appropriate agents to add in with metformin."	Thank you for your comment. The results of CANVAS have been added and DECLARE-TIMI is identified as ongoing.

		Janssen and Napp propose that reference be made here to the anticipated read out dates for the cardiovascular safety trials for canagliflozin (the CANVAS Program, showing as completed on clinicaltrials.gov) and due to present on Monday 12th June, 2017 at the ADA. Also, dapagliflozin (DECLARE-TIMI, expected study completion date April 2019) Janssen and Napp also request that reference be made to the CVD-REAL study which demonstrated that in a large real-world study across six countries and a broad population of patients with Type 2 diabetes, treatment with SGLT2i versus other glucose lowering drugs was associated with marked reductions in: Hospitalization for heart failure, all-cause death and hospitalization for heart failure or all-cause death. This will also present at the ADA on Tuesday 13th June, 2017 References: • *CANVAS Program clinicaltrials.gov https://clinicaltrials.gov/ct2/results?term=canvas&Search=Search (last accessed 22/05/2017)* • *DECLARETIMI clinicaltrials.gov https://clinicaltrials.gov/ct2/results?term=declare-timi&Search=Search (last accessed 22/05/2017)* • *CVDREAL http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190 (last accessed 22/05/2017*	This was published in May 2017, therefore not identified by the SIGN literature searches. As an observational study it is not regarded as eligible to answer the key questions.
Section 11			
General	RCPL	Guidance on insulin and SU combination.	The discontinuation of sulphonylureas is implied by the preceding text but we agree this may be insufficiently clear. A GPP has been added "Consider stopping or reducing sulphonylurea therapy when insulin therapy is initiated."
	AG	The advice given is fairly sound and affords flexibility in choice rather than being proscriptive. This highlights the acknowledgement that an individual approach to insulin initiation is frequently required. I'm happy with the advice given and the way the guideline has been carefully considered.	Thank you. Noted.
	AB	Agreed.	Thank you.

	MC	Why would a disease that is associated with insulin resistance be treated with insulin? High insulin levels are associated with cancer, cardiovascular disease and obesity.	Type 2 diabetes is associated with insulin resistance, but also β-cell dysfunction. Weight loss and some other agents used in the treatment of type 2 diabetes (metformin, pioglitazone) can improve insulin sensitivity. However, over time, these become less effective and insulin can be necessary to maintain blood glucose control, even at the expense of weight gain. As the reviewer mentions, insulin therapy can cause or exacerbate obesity. The suggestion that insulin might cause cancer and/or cardiovascular disease is speculative and there is much evidence to the contrary.
	FG	Are gallstones a firm CI to GLP1? – Not in BNF.	The SPC and BNF for liraglutide have changed since the first draft of this guideline, so we have removed the reference to gallstones.
	RCP	Clearly written section.	Thank you.
	ME	The absence of the SWITCH 1 and 2 data with respect to informing this guideline represents a significant limitation. these data clearly illustrate the cost effectiveness of insulin degludec in hypoglycaemia prone patients vs. Insulin glargine, with degludec being dominant (more effective and cheaper) in type 1 diabetes	SWITCH 1 was conducted in patients with type 1 diabetes only. The data from SWITCH 2 may be relevant to this guideline on type 2 diabetes, but were published outwith the search period. However, we are able to use data from the DEVOTE cardiovascular outcome trial in type 2 diabetes, in which prespecified adjudicated severe hypoglycemia occurred in 187 of 3,818 patients (4.9%) in the degludec group and in 252 of 3,819 patients (6.6%) in the glargine group, an absolute difference of 1.7 percentage points (rate ratio, 0.60; P<0.001 for superiority; odds ratio, 0.73; P<0.001 for superiority). *Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr PM, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB; DEVOTE Study Group. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1615692. [Epub ahead of print] PubMed PMID: 28605603.*
	JM	Satisfactory.	Thank you.
	Sa	We would like to request for greater consistency and balance regarding ICER / QALY data as this is the only therapy in the draft guidelines that is subject to this analysis.	Noted. Cost-effectiveness data were included in SIGN 116 as the evidence generated by literature searches contained such data. It seemed appropriate that cost-effectiveness data should be updated to include the new

			insulins. ICER data are available for other more costly therapies e.g. GLP-1s but estimates are imprecise. e.g. Zueger PM, Schultz NM, Lee TA. Cost effectiveness of liraglutide in type II diabetes: a systematic review. Pharmacoeconomics. 2014 Nov;32(11):1079-91. Rather than providing cost-effectiveness data for a wider range of agents, we have complied with a request from SMC that the previously included cost effectiveness data are removed.
	DS	There is a need to emphasise the importance education around the time of insulin initiation. This is very critical in ensuring good injection technique, hypo management, lifestyle changes etc	The reviewer is of course correct. However, the evidence base for this guideline update was generated by searching the literature on the basis of key questions plus incorporating evidence from NICE and AHRQ. SIGN 116, which contained information about management of type 1 and 2 diabetes including advice on injection technique and timing. NICE includes the following non-evidence-based recommendation: "When starting insulin therapy in adults with type 2 diabetes, use a structured programme employing active insulin dose titration that encompasses: • injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites • continuing telephone support • self-monitoring • dose titration to target levels • dietary understanding • DVLA guidance (At a glance guide to the current medical standards of fitness to drive) • management of hypoglycaemia • management of acute changes in plasma glucose control • support from an appropriately trained and experienced healthcare professional. [2015] " Key points reflecting advice from NICE and SIGN 116 have been added to the Provision of Information section.
11.1	AG	See above.	Thank you.

	AB	I think your recommendation should include a firm statement to stop sulphonylureas when starting insulin because of the dangers of hypoglycaemia	The discontinuation of sulphonylureas is implied by the preceding text but we agree this may be insufficiently clear. A GPP has been added: “Consider stopping or reducing sulphonylurea therapy when insulin therapy is initiated.”
	SB	P27. 11.1. R. Does the recommendation to continue metformin, mean that other orals should be withheld? This is unclear.	See comment above. As some other oral therapies are licensed for use with insulin, we believe a blanket statement to that effect would be too strong, other than the caveat regarding sulphonylureas. The algorithm clarifies coprescribing of glucose-lowering drugs with insulin.
	SMac	Common practice.	Thank you.
	ME	This is appropriate.	Thank you.
	JM	Satisfactory.	Thank you.
	NovNo	The recommendation in this section is unclear as to what action to take for any other agents. Suggested wording for the recommendation could be: "Oral metformin therapy should be continued when basal insulin therapy is initiated to maintain or improve glycaemic control and the continuation of other non-insulin agents should be reviewed". We also suggest that the title of this section is amended to read: "Continuing non-insulin agents when initiating basal insulin"	We have added a Good Practice Point “the continuation of other non-insulin agents should be reviewed”. Changing the wording from “oral to “non-insulin would extend this recommendation to imply discontinuing GLP-1 therapy when insulin is initiated. This may not always be appropriate.
11.2	AG	See above.	Thank you.
	AB	Whilst it is difficult to disagree with your recommendations from a health economic perspective, it seems to me perverse and may be even against Hippocratic principals to recommend waiting until hypoglycaemia occurs before allowing an insulin with a lower risk of hypoglycaemia to be used. Hypoglycaemia (and blindness) is the greatest fear of people with insulin treated diabetes	The wording of the recommendation is intended to allow prescribers a degree of flexibility to recommend forms of basal insulin they believe from clinical judgement to be necessary. This is the approach that has been used successfully and apparently without ethical concerns in Scotland for the last seven years.
	SB	Suddenly this section is dominated by cost calculations, which have been much less obvious elsewhere. Should there be consistency throughout?	See above (Sa response)
	FG	Titration targets in ref 104: 4.4 to 5.5 mM – it is incredible that we consider these types of studies in any way reflective of normal T2DM management. Has anyone ever titrated NPH / Lantus to <5.5mM in someone with T2 diabetes in Scotland!? I think this point needs made about all	The text summarises the 4T study, a collaboration between academia and industry. It is not intended to imply what is “normal management.”

		titration studies where pharma are looking to prove the superiority of their insulin analogues in terms of hypoglycaemia.	
	SMC	Paragraph 4 referring to insulin glargine and insulin degludec. The first two sentences should read "…accepted for use by SMC", rather than "approved by SMC". The remainder of this paragraph that refers to the cost-utility analysis, costs and QALYs should be removed from the guideline. This information is included in the published SMC advice and it would be more appropriate to reference the SMC advice so that readers can refer to the SMC advice it its entirety. The published SMC advice for insulin degludec refers to insulin glargine as the comparator and doesn't specify whether this is the originator product or the biosimilar so including this detail in the guideline inadvertently releases commercial in confidence information. In addition, this information has not been included for any other medicine classes included in the guideline, so it appears inconsistent to include such details in this section. The sentence relating to the SMC policy on biosimilars and falling cost of the comparator is speculative and should not be included in the guideline.	Noted. This has now been removed. Noted. This has been removed. Thank you. This has been removed.
	ME	Insulin initiation with intermediate-acting insulin represents a reasonable clinical and economic consideration.	Thank you. Noted.
	JM	Satisfactory.	Thank you.
	Sa	Degludec has been compared to 'insulin glargine'. Please be specific as to which insulin glargine this is referring to. In this case, it is insulin U100. We would like to request for greater consistency and balance regarding ICER / QALY data as this is the only therapy in the draft guidelines that is subject to this analysis. We would also like to request for more clarity around the following statement: 'Careful clinical judgement must be applied to ensure insulin therapy is not delayed inappropriately' [2nd paragraph, page 32]. The section relating to insulin being 'delayed inappropriately' does not	Thank you for this comment – the text was carried over from the SIGN 116 at which time there was only one formulation of insulin glargine. The concentration has been added. See above. (ICER/ QALY data have been removed) The wording in this Good Practice Point refers to a clinical judgement rather than a timescale – i.e. the time will vary amongst individual patients.

		intimate a time scale or appropriate metrics. This further information would considerably assist patients and physicians in the management of diabetes.	
	NovNo	The information in this section include data comparing analogue insulins and therefore the title may be better simply as "Initiating basal insulin".	Noted. The evidence summarised is that which underpins the contemporary strategy of initiating basal first as opposed to twice daily or prandial insulin, however, for clarity we have renamed the title.
		The BEGIN trials comparing insulin degludec to insulin glargine U100 are included however it does not include the double-blinded RCT of SWITCH 2 where the primary end point was a difference in hypoglycaemia rates. SWITCH 2 has recently been added to the insulin degludec SmPC (1). In this 64-week controlled, double-blind, randomised, cross-over, treat to-target trial, 721 patients with at least one risk factor for hypoglycaemia were randomised to either insulin degludec or insulin glargine (100 units/mL) followed by cross-over. The primary endpoint of confirming superiority of insulin degludec compared to insulin glargine in the rates of severe or blood glucose symptomatic confirmed hypoglycaemia during the 16 week maintenance period was achieved (30% lower rate of severe or blood glucose confirmed symptomatic hypoglycaemia; estimated rate ratio of 0.70, (95% CI 0.607 to 0.801, p<0.0001).	See comments above.
		In this section, the guideline includes health economic aspects of insulin degludec in the form of ICER data. It seems less suitable and inconsistent to mention this in a primarily clinical evidence based practice guideline where this is the only mention of an ICERs in the document. Furthermore, if it is decided to retain the health economic data for insulin degludec, please be aware that the most relevant patient population for this section of the guideline is the population on a basal-only regimen (in this case the ICER (versus insulin glargine) is dominant. The ICER that is currently reported relates to the basal bolus population. (2)	See above. (ICER/ QALY data have been removed)
		The recommendation for considering basal insulin analogue is guided by the statement "according to the level of concern regarding hypoglycaemia risk" This is an imprecise statement which may	Noted. We have revised the wording of the recommendation to “considered according to hypoglycaemia risk” to emphasise that we are not referring to a quantifiable risk threshold.

		be interpreted differently by healthcare professionals. We suggest that the statement reflects the existing NICE guidance. We acknowledge that the statement is included in Section 13 but we believe it should be appropriately included at this point in the guidelines, with the additional inclusion of insulin degludec as outlined in our recommendation for section 13.1. *1. Novo Nordisk Limited; Tresiba SmPC* *2. SMC. 2nd Resubmission* *insulin degludec (Tresiba®) 100units/mL solution for injection in prefilled* *pen or cartridge and 200units/mL solution for injection in pre-filled pen* *SMC No. (856/13) Available from:* *https://www.scottishmedicines.org.uk/files/advice/insulin_degludec_Tresiba_2ndResub_FINAL_July_* *2016_Updated_30.07.16_for_website.pdf* *[accessed May 2017]*	
	NHSsig	SMC restrict glargine u100 & u300 to patients who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections. Degludec was accepted as it was non-inferior to other analogues, the above restrictions will apply to degludec as they do to glargine. I would suggest the recommendation is amended to reflect this rather than a perceived risk of hypoglycaemia. The consequence is that analogue prescribing will be the norm. It is also important to note that patients with severe hypoglycaemia & *[incomplete comment]*	The recommendation has been updated to: “Once daily bedtime NPH insulin should be used when adding insulin to metformin. Basal insulin analogues should be considered according to hypoglycaemia risk, for example, patients who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections.”
	ABPI	The statement “careful clinical judgement must be applied to ensure insulin therapy is not delayed inappropriately” is open to interpretation and more consideration could be given to being directional as to the meaning of the term “clinical judgement”, the time frame which would be considered “inappropriate” and this also requires further clarity.	The wording in this Good Practice Point refers to a clinical judgement rather than a timescale – i.e. the time will vary amongst individual patients.
11.3	AG	See above.	Thank you
	AB	In your recommendations I think you should add "....or a GLP-1 receptor agonist"	This recommendation concerns initiating insulin therapy. Initiating GLP-1 therapy, whether alone or in combination with insulin, is considered in section 8. Please also see the algorithm (now added).

	SB	I am confused why a basal-plus regime (i.e. addition of prandial insulin) is seen as preferable to the addition of a GLP-1RA? There is a literature out there that should have been considered.	We identified two trials of sufficient size: Diamant (blinded), HR -0.03 (-0.17 to 0.11) and Rosenstock (open-label) HR -0.16 (-0.33 to 0.01). The published evidence is therefore not consistent with superiority of adding a GLP-1 RA over adding prandial insulin in this context. The GDG is aware that there are unpublished data suggesting that this may be the case for the combination of liraglutide and degludec (as fixed-dose Xultophy) vs glargine and aspart basal bolus but unpublished evidence cannot be considered.
	JM	Satisfactory.	Thank you
	Sa	Request that the phrase 'more concentrated' is removed in reference to glargine U300. This is potentially misleading as Toujeo has a flatter profile than Lantus. Toujeo has less hypoglycaemic events and is longer lasting compared to Lantus (references: EDITION study programme, Heise 2015 study). The current terminology implies that glargine U300 is a treatment for obese patients who require higher doses.	Disagree - It is incontrovertible to state that U300 is more concentrated than U100. This statement is not intended to imply anything additional about pharmacokinetics or pharmacodynamics, or any restriction or extension of indication.
11.4.1	AG	See above.	Thank you
	AB	Agreed.	Thank you
	FG	Basal + is better but only mentioned in the initiation section – shouldn't 11.3 and 11.4 be combined? The practice point 'Aim to optimise…' is fairly self-evident. Significant issue of tight titration targets in studies showing expensive insulins are better.	The two sections both draw on different elements of the 4T study (one year and three year follow-up). The section structure was carried over from SIGN 116. We do not think that combining would improve clarity. The inclusion of this statement in SIGN 116 may have helped health care professionals to appreciate a principle that now seems more "self-evident" than it did then. We are limited to summarising the evidence from the trials that have been conducted using the targets to which the reviewer refers.
	JM	Satisfactory.	Thank you
11.4.2	AG	See above.	Thank you
	AB	Agreed.	Thank you
	SB	P29. 11.4.2. The comments regarding soluble versus rapid-acting analogue insulins doesn't seem to take into account	The text of the guideline is a summary of the evidence for the various treatments (including insulins) in relation to the

		the need for an injection for a longer period pre-meal. No guidelines would suggest soluble insulin for people with type 1 diabetes who are being advised to use a basal-bolus insulin regime - why would this be different for people with type 2 diabetes??	outcomes specified in the key questions (in this case HbA1c reduction). To our knowledge, there is no evidence of a difference between soluble and analogue insulin for this outcome in type 2 diabetes, although as the reviewer suggests, timing of injection makes rapid-acting analogues an attractive option for many individuals. Advice for injection timing in relation to meals are given in the Provision of Information section.
	JM	Satisfactory.	Thank you
	NovNo	We would like to make you aware of a new generation of bolus insulin analogue, faster aspart, which is now available for the treatment of diabetes with an improved PPG increment at one hour in type 2 diabetes patients compared to existing bolus insulin analogues. (1) This insulin has been submitted to the SMC and has been approved though an abbreviated submission for use in type 1 and type 2 diabetes in Scotland. *1. Bowering K et al. Faster aspart versus insulin aspart as part of a basal–bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial; Diabetes Care; DOI: 10.2337/dc16-1770.*	Noted. We are aware of faster aspart. We believe that the current text applies appropriately. The reference cited demonstrates non-inferiority of faster aspart vs aspart.
	EL	Please be aware that insulin lispro is also available as an option. Insulin lispro (Humalog KwikPen) is available in two strengths. For both, the needed dose is dialled in units. Both pre-filled pens, the Humalog 100 units/ml KwikPen and the Humalog 200 units/ml KwikPen deliver 1 – 60 units in steps of 1 unit in a single injection. The number of units is shown in the dose window of the pen regardless of strength and no dose conversion should be done when transferring a patient to a new strength. Insulin lispro 200 units/ml solution for injection was bioequivalent to insulin lispro 100 units/ml solution for injection after subcutaneous administration of a single 20 unit dose in healthy subjects. Time to maximum concentration was also similar between formulations. Humalog 200 units/ml KwikPen should be reserved for the treatment of patients with diabetes requiring daily doses of more than 20 units of rapid-acting insulin.	The evidence summary and recommendations do not name insulin lispro or any other rapid-acting analogue insulin.

		The insulin lispro solution containing 200 units/ml should not be withdrawn from the pre-filled pen (the KwikPen) or mixed with any other insulin. (Humalog 200 Units/ml KwikPen, solution for injection in pre-filled pen (2016). Summary of Product Characteristics (SmPC). EMC, available at https://www.medicines.org.uk/emc/medicine/30005; Humalog KwikPen 100 units/ml, solution for injection (2017). Summary of Product Characteristics (SmPC). EMC, available at https://www.medicines.org.uk/emc/medicine/9314)	
Section 12			
General	RG	The research is available for all to see – including that found in SIGN 115. A gastric bypass is effective in a majority of cases for stopping diabetes type 2.	Thank you, but this relates to lifestyle management and is not relevant to the current guideline.
	AG	A good summary of the guideline for patient and carer alike. Good to have acknowledged Diabetes in Scotland, DUK, DVLA, Health Talk and My Diabetes My Way.	Thank you
	AB	Agreed.	Thank you
	GB	There were omissions of information for the individual drug groups and they did not seem to be consistent with the information given.	Unclear which omissions are intended. This section provides general information about important practical issues associated with use of each class of drugs.
	SB	I wonder if the guideline could define the term 'open attitude of unconditional positive regard'? Metformin. Suggestion: Patients should be advised that bowel upset can begin at any stage of their metformin treatment, without their being a change in dose. If there is use of slow release preparations due to intolerance of standard metformin, then the slow release version should be used in divided doses (rather than once daily). These are guidelines based on clinical experience; if they are not to be included, then the guideline can be shortened to 'consult the SPC of each medication'. Metformin should ALWAYS be discontinued during a severe illness. 'Sick	This describes a positive and non-judgmental approach. It does not have a specific definition beyond the direct sense of the phrase itself. It has been simplified to “open attitude”. Thank you. While this is true, we do not believe that providing this information will prevent harm and may induce misattribution of unrelated GI disturbances to metformin use. If patients report GI disturbance, this can be managed appropriately depending on individual circumstances. The potential to divide dose of modified release metformin is contained in the SPC and we have clarified this option. Agreed. This has been revised.

		day' rules need to be emphasised, especially since the disproportionate weight given the 342 UKPDS patients (see above), leads to metformin often being the anti-glycaemic agent that patients continue to take...	
		Sulphonylureas. I am surprised to see an EU country proposing a guideline that includes glibenclamide. This makes NICE look thoroughly modern.	Noted. This has been removed.
		Most patients with type 2 diabetes will need to 'avoid calorie excess', not just those on an SU.	Noted. This has been removed.
		GLP-1RAs. The text implies HbA1c testing in the 'first weeks' of use. Is this the recommendation?	This section provides general information about important practical issues associated with use of each class of drugs, rather than recommendations.
		The bit about Ramadan is totally confusing - "multiple preprandial injections"???	Noted. This has been revised for clarity.
		If pancreatitis is going to be mentioned here (I don't think it should be) then it needs to be included in the DPP-4 section.	Noted. This has been removed.
		Acarbose now comes after the GLP-1 RAs, which I think it should. But for consistency, the order should reflect that in the previous text (which I would change).	This has now been removed from the guideline.
		Insulin. Some comments: Why not just assume that any patient with a tight HbA1c target (e.g. younger patients) will need twice daily NPH insulin and thus recommend basal analogue insulin?	Thank you. These are general comments and not specifically relevant to Provision of Information.
		What sort of patient wouldn't want to inject insulin immediately before a meal??	Noted.
		It seems odd to see the major focus on U300 glargine and no mention of degludec (with its much larger published database). There was a similar mismatch with fixed ratio insulin-GLP-1RA combinations earlier in the guideline. This needs to be addressed.	This section emphasises important considerations for practical use of the drugs. Evidence for effectiveness/safety of fixed ratio degludec and liraglutide is presented in section 8.1.5 and 8.2. The potential for misdosing between U300 and U100 glargine is a significant practical issue which warrants inclusion in this section.
		SGLT2 inhibitors. The initial focus on DKA for this class may be over-played since there is uncertainty as to whether this really is a side-effect of these drugs.	Noted. The warnings published by MHRA and included in the BNF are for all SGLT2 inhibitors.

		There should be a differentiation between mycotic genital infections and UTIs; again there is uncertainty as to whether UTI really is increased with this class of drugs. I would suggest that sick-day rules apply to SGLT2 inhibitors (and GLP-1RAs) in the same way as they should with metformin.	Noted. The word “urinary” has been removed from the description of possible infections. Noted.
	MC	No information about diet.	Diet as a treatment for type 2 diabetes is covered in SIGN 116.
	FG	Where is evidence that MR metformin is better in respect to GI side effects? Also not mentioned in main metformin section. Do these contrast restrictions have a firm evidence base?	No new evidence was reviewed for the effectiveness of metformin. The advice from the Royal College of Radiologists has been archived during the development of this guideline. Current advice from the Royal Australian and New Zealand College of Radiologists has been considered instead.
	BK	As before a summary table of the different classes of drugs comparing HbA1c reduction, side effects such as weight and hypos, CVD outcomes etc would be useful. I'm not sure if this has been planned or not.	Thank you. The algorithm provides such a summary.
	AGo	There are very few references to the need for blood glucose monitoring in relation to driving. On page 32 there is a minor comment but the most important issues have been omitted. As both DVLA and NICE recommend blood glucose monitoring in patients on sulphonylureas with a Group 1 licence this should be included. For those with Group 2 licences monitoring is mandatory on sulphonylureas. The information from the table Assessing Fitness to Drive would be useful to include and the reference provided should be Assessing Fitness to Drive.	Thank you. Further information about hypoglycaemia risk and a cross reference to the DVLA requirements have been added to the sulphonylurea subsection of the Provision of Information section.
	RCP	Well written, clear.	Thank you
	JM	Satisfactory.	Thank you
	SM	Information is useful for Patients and carers. Additional information that would be helpful could include the need to access local information about adjustments to therapy for investigative procedures that include fasting or reduced oral intake.	Thank you. This section is intended for healthcare professionals to use in consultation with patients and carers.

	DS	Provision of information on Pioglitazone: The conversation on the risks associated with Pioglitazone should also include increased risk of bladder cancer and heart failure.	Thank you. These have been added.
	ABPI	In the SGLT2 section, we agree it is important to highlight the small risk of DKA when using this class of drugs however, this should be contextual to other side effects in terms of magnitude	Thank you. Agreed.
	JN	Individuals who are prescribed SGLT2 inhibitors should be made aware of the risk of DKA and how to recognise the symptoms…." Janssen and Napp consider that without context, the statement regarding DKA could be misinterpreted. We suggest the risk of SGLT2 inhibitor DKA be quantified as in the SmPCs for all SGLT2 inhibitors, which state the risk is 'rare' (≥ 1/10,000 to <1/1,000). We also suggest that a link be provided to the ABCD position station of SGLT2 inhibitors and DKA, for anyone wanting further information Reference: •*Canagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28400 (last accessed 22/05/2017)* •*Empagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/28973 (last accessed 22/05/2017)* •*Dapagliflozin SmPC: https://www.medicines.org.uk/emc/medicine/27188 (last accessed 22/05/2017)* 4.4 Special warnings and precautions for use Diabetic ketoacidosis Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including canagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl). It is not known if DKA is more likely to occur with higher doses of canagliflozin. The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients	Thank you. We have added a link to this position statement.

		should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. • *ABCD SGLT2 inhibitors & DKA position statement: http://www.diabetologistsabcd.org.uk/Position_Papers/ABCD_DKA_SGLT2.pdf (last accessed 22/05/2017)*	
Section 13			
13.1	AB	I think you need to be even stronger in this section when emphasising the risks of hypoglycaemia with sulphonylureas and that good alternatives are available. Why do you keep on referring to DPP-4 inhibitors and GLP-1 Receptor agonists as "newer" agents? These drugs have been available for over 10 years and have been used in millions of patients. This wording gives the impression of "less tested" or "more dangerous" when in fact there have been far more (safety) studies with them than with the "older" agents. I would recommend reduction OR STOPPING sulphonylurea when adding a GLP-1 RA. Worth mentioning CV protection with SGLT2 inhibitors?	This section is for providing advice to patients and informing discussions about practical issues. Agreed. This may be due to some text being retained from a previous version of the guideline. This terminology has been revised. Noted. The advice “dose of concomitant sulfonylurea may need to be reduced” is included in the British National Formulary entries for GLP-1 receptor agonists. There is no specific advice for stopping sulphonylureas. This information is contained in section 9 of the guideline. The provision of information section contains practical advice for administration of the drugs.
	ABI/EL	You might consider aligning the order of the medication class with the one in the TOC. Not included but should be – Renal Impairment use of DPP4i given limitations of other classes in this area (also could be added to section 7).	Thank you. This has been corrected. This section contains advice which healthcare professionals may consider passing on to patients regarding use of these drugs. The dose reductions suggested for individuals with renal impairment are not considered part of this advice, but should be considered by the professional in charge of prescribing for the affected individual.
	SMac	Excellent, salient points.	Thank you.
	AGo	Driving/Insurance and Informing the DVLA should be included.	Thank you. Further information about hypoglycaemia risk and a cross reference to the DVLA requirements have been added to the sulphonylurea subsection of the Provision of Information section.
	JM	Satisfactory.	Thank you.
	AZ	AstraZeneca would like to add to the guidance that fixed dose combinations	Noted. Advice on fixed dose combinations is already included in

		(FDCs) should be used with eligible patients in oral therapy where available and either cost neutral or cost saving, to reduce pill burden and enhance compliance. AstraZeneca suggests that the overall section 13.1 balance may be further improved, for example sections on thiazolidinediones and DPP4-inhibitors seem light in content. Specific comment to section 13.1 We would like to add the following to the SGLT2-inhibitor section [from the Medicines and Healthcare Products Regulatory Agency (MHRA)] Canagliflozin may increase the risk of lower-limb amputation (mainly toes) in patients with type 2 diabetes. Evidence does not show an increased risk for dapagliflozin and empagliflozin, but the risk may be a class effect. Preventive foot care is important for all patients with diabetes. Available from: https://www.gov.uk/drug-safety-pdate/sglt2-inhibitors-updated-advice-on-increasedrisk-of-lower-limb-amputation-mainly-toes. We also note that the Food and Drugs Administration (FDA) has on May 16th strengthened its warning on amputations with regards to canagliflozin, including a boxed warning, to be added to the canagliflozin drug labels. Available from: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm558605.htm For dapagliflozin please refer to: Recently published data on the incidence of amputations across 30 pooled studies for dapagliflozin shows: Lower limb amputation was identified in 8 (0.1%) and 7 (0.2%) patients in the DAPA (N=9,195; 8,059 patient-years) and PBO (N=4,629; 4,177 patient-years) groups, respectively Reference: *The incidence of amputation in the dapagliflozin clinical trial program. Jabbour S, Seufert J, Scheen A, Karup C, Langkilde AM.*	section 13.1 "A number of oral agents are available in combination with each other in fixed dose combination. Using these preparations to decrease 'tablet burden' is convenient, and moreover is associated with increased concordance with therapy." The TZD class only includes a single agent, while DPP-4 inhibitors are generally well tolerated. The EMA/MHRA assessments of the safety of SGLT2 inhibitors is included in section 8.2. Information on risks of amputation have been added, alluding to the CANVAS trials and the EMA assessment.

		Poster presentation 119. Endocrine Practice 2017;23 (1): pp. 46A.	
	NHSGGC	Under the section on INSULIN - Should there be a line at the beginning to say that 'Patients starting / taking Insulin will need specific information on diet, meal timings and avoiding the risk of hypoglycaemia' as it only mentions this in regard to Ramadan and it also mentions meal timings in regard to metformin and sulphonylureas and seems pertinent to also have this at the Insulin section.	Agreed.
	NovNo	Under the insulin section where it is stated individuals for whom basal analogues may be appropriate over NPH basal insulin as those who need assistance from a carer or healthcare professional to inject their insulin, the analogues insulin detemir and insulin glargine are mentioned but not insulin degludec. Insulin degludec is a once-daily insulin with a half-life of approximately 25 hours allowing for flexibility in the timing of insulin administration on occasions when administration at the same time of the day is not possible.(1) We suggest insulin degludec is included alongside the other analogue insulins here. This section also gives guidance from the glargine U300 SmPC recommending reductions in the dose by 20% when transferring to insulin glargine U100. The revised insulin degludec SmPC now also states that a dose reduction of 20% should be considered when transferring to degludec from insulin glargine (300 units/mL) or twice-daily basal insulin.(1) *1. Novo Nordisk Limited; Tresiba SmPC*	Thank you. We have revised this to "basal analogue insulin", therefore removing any reference to specific insulins.
	ABPI	In the SGLT2 section, we agree it is important to highlight the small risk of DKA when using this class of drugs however, this should be contextual to other side effects in terms of magnitude	See above. A link to the Association of British Clinical Diabetologists position paper has been added for further details.
	NHSsig	We found this section as it was written rather odd for inclusion in SIGN. Importantly statements are included which are not referenced nor the evidence assessed. Clinicians refer to SIGN documents as an evidenced based resource and the inclusion of some of the recommendations here seem less than robust. The title is "a checklist for provision of information for issues of most concern to families and patients" It is not a checklist. It further includes information one would	Provision of Information is included in every SIGN guideline and contains practical advice to inform the healthcare professional in their consultations with patients to help facilitate the recommendations. It is developed based on the clinical experience of the GDG with reference to relevant national guidance. The title of the section is standard to all SIGN guidelines. It is a checklist in so far as it is a list of drug classes with key practical information about the use of

		expect in a Prescribing Strategy and not a guideline eg NPH insulin.	each which may be 'dipped into' as appropriate during consultations with patients. The more usual checklist arranged by stages of care is less appropriate for this guideline, as the focus is on classes of drugs, rather than progression through diagnosis, assessment, treatment and follow up stages. The SIGN guideline will be used alongside the forthcoming Scottish Diabetes Prescribing Strategy and their content will be complementary.
		It further states it is not exhaustive nor exclusive which is a failing. If written generically as a checklist this is overcome and accuracy, evidence base are overcome but the points that are important are highlighted ie potential side effects,	See above.
		Cost effectiveness needs to be considered in the development of the guideline. Combination therapies and MR preparations would not necessarily be a general recommendation. Managing tablet burden, considering effectiveness of treatment and stopping tx that is ineffective should be part of that wider consideration. The application of Realistic Medicine & Polypharmacy Guidance as national strategies could be considered for referencing in such a situation.	Due to the rapid review methodology adopted, cost effectiveness was not included as an outcome for the key questions. Each of the factors listed by the reviewer will be addressed by the Scottish Diabetes Prescribing Strategy.
		For example, in the full NICE guidance wrt sulphonylurea MR preps the GDG noted the limited 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 tablets 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. (p193) If facts are being stated they should reference the evidence and also the quality of the evidence.	The SIGN guideline did not include key questions which directly compared the effectiveness of drugs within classes. It is a rapid review of one section of SIGN 116.
		I would also suggest there is consideration of Realistic Medicine in this section as well as the importance of diet and lifestyle advice throughout given the	'Realistic Medicine' as a conceptual framework for combining evidence with relevant clinical experience to produce optimal outcomes for patients has been a

		impact of low carbohydrate/low cal diets on diabetes progression.	principal on which SIGN guidelines have been based for 25 years. Diet and lifestyle advice are outwith the remit of this guideline, but are contained in SIGN 116.
		Where there is concern about the number of meds consideration should be made to those that may no longer be working and de-prescribing considered. Relaxation of control depending on patients' comorbidities and life expectancy.	Noted. These are general principals of prescribing and are addressed in the algorithm which suggests individualised targets and stopping rules for all drugs.
		I think there is a more positive patient centred statement that could be included under principles. The following is taken from NICE. "Adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long term interventions because of reduced life expectancy. Such an approach is especially important in the context of multimorbidity. Reassess the person's needs and circumstances at each review and think about whether to stop any medicines that are not effective."	Noted. This statement has been expanded.
		"As for oral agents, people taking GLP1 may hold a regular licence without restriction." If including this information it is not factually correct as type 1 licence holders are required to advise DVLA if they have a hypo needing assistance. This may occur is someone is on an SU and a GLP1.	Agreed. Further information and a cross reference to the DVLA requirements have been added to the sulphonylureas section and this statement has been qualified with "some oral agents".
		Increasingly I feel this section is best converted into a checklist with the themes taken from the text, as omission and making this section robust despite the caveat (of not exhaustive) is not acceptable in a guideline of this standing. The ACS guidance does this well.	Given that the remit of this guideline is only pharmacological management of glucose control in patients with type 2 diabetes, the provision of information section focuses on each class of drugs which are included in the guideline. Unlike NICE, it does not cover the full spectrum of diabetes. SIGN 116 contains recommendations for diet and lifestyle management in diabetes. SIGN 148 (ACS) had a wider remit which covered many stages of care for people with acute coronary syndrome.
13.2	AB	Agreed.	Thank you
	MC	Why no mention of diabetes.co.uk?	Thank you. The GDG did not find it to be sufficiently independent.
	AGo	DVLA – Assessing Fitness to Drive.	Thank you. While this website is for healthcare professionals only, we have

			amended the link in the guideline to https://www.gov.uk/diabetes-driving which is targeted to individuals with diabetes (the purpose of this section).
	ME	As discussed the results of the DEVOTE and CANVAS studies would be informative as would the SWITCH 1 and 2 studies	Thank you.; This section is for general sources of information for patients, rather than RCTs.
	JM	Satisfactory.	Thank you
	DS	The DVLA is referenced as a source of further information but their driving regulations around the use of insulin and glucose lowering drugs may need to be made more explicit.	Thank you. Further details have been added to the Provision of Information section with a cross reference to the Assessing Fitness to Drive information for healthcare professionals. In addition, the general advice from DVLA to people with diabetes is now referenced in section 12.2 (revised numbering).
Section 14			
General	AG	I don't feel there is much need for comment from me here. The guideline implementation process etc has been very carefully considered over the lifetime of SIGN. It follows a well worn and effective path.	Thank you
	AB	Agreed.	Thank you
	JM	Satisfactory.	Thank you
14.1	AB	Agreed.	Thank you
	JM	As the management of people with type 2 diabetes is increasingly within primary care, the implementation strategy needs to ensure that GPs and Community DSNs are actively involved in its implementation.	Agreed
14.2	AB	Agreed.	Thank you
	JM	Satisfactory.	Thank you
	Ta	The direct prescribing costs for diabetes are increasing and reached close to £90 million for NHS Scotland in FY2015. This compares to £79 million the previous year, and £75 million in FY2013, meaning over the past three years, NHS Scotland has spent almost £250 million on drugs to treat diabetes.(1) The total spend (increasing by 18% since FY2013) has increased at a greater rate than the number of prescriptions (increasing by only 7% since FY2013) suggesting a trend towards the prescription of more costly treatments in diabetes. Below is the cost of prescribing drugs for the treatment of diabetes for the last three years, and the number of items	Thank you. SMC provides advice based on the budget impact of individual agents. Furthermore, the Scottish Diabetes Prescribing Strategy will follow this guideline and present an evidence-based template for appropriate prescribing, taking into account the cost implications of treatment on a national level.

		dispensed. FY2015 – 3,572,939 at a cost of £88.97 million FY2014 – 3,448,522 at a cost of £79.43 million FY2013 – 3,340,313 at a cost of £75.67 million Source: ISD Scotland. Alogliptin is now used in half of Scottish Health boards as the first line DPP-4 inhibitor option for the treatment of Type 2 diabetes for appropriate patients. Alogliptin is 20% less expensive than the most commonly prescribed DPP-4 inhibitors (NHS list price).(2) Alogliptin therefore helps NHS Scotland meet the 2014-2016 Scottish Diabetes Prescribing Strategy objective: "The purpose of this strategy is to ensure person-centred, Evidence-based, quality, safe and cost-effective prescribing for people living with type 2 diabetes" Alogliptin enables NHS Scotland to realise cost savings, not only in new patients, but via medicines optimisation programmes for existing patients as well. This is especially significant given the rapidly increasing costs associated with prescribing newer treatments. For example the primary care prescribing costs of SGLT2 inhibitors in Scotland increased by £2.4M in the 12 months to February 2017 and reached £5M over the year (Source: The Information Services Division of NHS National Services Scotland, last accessed May 2017 for February 2017 data). It is therefore important that Health Boards across NHS Scotland are directed by SIGN guidelines to consider budget impact in determining prescribing strategies in Type 2 diabetes. Given the substantial and rising proportion of the NHS Scotland budget spent on prescribing in diabetes, we recommend that SIGN include recommendations based specifically on cost impact (both between classes and within class of therapy) in order to encourage rational and cost-effective prescribing.	

		1. https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Publications/2016-07-12/2016-07-12-Prescribing- *PrescriptionCostAnalysis-Report.pdf Last accessed May 2017.* *2. NHS Business Services Authority, Drug Tariff Part VIIIA. Available at http://www.drugtariff.nhsbsa.nhs.uk/ Last accessed May 2017.*	
14.3	AB	Agreed.	Thank you
	ME	Auditing clinical outcomes as a function of expenditure would be highly informative.	Agreed.
	JM	Satisfactory.	Thank you
14.4	ME	Traditional cost effectiveness evaluations supported by budget impact and real world data would be of use.	Noted. The rapid review methods used in this update did not allow these to be conducted de novo, and cost effectiveness was not included in the AHRQ methodology. However, data from the NICE NMA is included, where appropriate. SMC provides budget impact analyses of approved medicines for NHSScotland.
	JM	Satisfactory.	Thank you
Section 15			
15.1	RCPL	Non RCT real life info of value.	Noted
	AG	Excellent researchers are employed to ensure every bit of appropriate literature is considered in a guideline. Needless to say the process has not changed for this update. I cannot think of any literature which should have and has not been included.	Thank you
	AB	Agreed.	Thank you
	SB	Often out of date and not done as well as one would expect of SIGN....	The rapid update process used in this guideline has made use of quality approved sources of collated evidence (NICE and AHRQ). This has been supplemented by further individual literature searches and inclusion of pivotal CVOTs up to September 2017. We are confident that the guideline reflects the most important recent evidence, and that compromises made to allow the rapid development have not significantly reduced the quality of the final product. Incorporation of extensive feedback from two separate consultation exercises has helped to reduce any potential gaps.
	BK	Good.	Thank you
	JM	Satisfactory.	Thank you

15.2	AG	Not included in draft.	Thank you
	AB	Agreed.	Thank you
	BK	It would be worth updating the Type 1 section on therapies etc given the significant advances in the technologies to better enable diabetes care. The role of many of these agents in the prevention of type 2 diabetes would also be an area of great interest given the focus on managing obesity and the national prevention strategy.	Noted. The reviewer can submit a proposal to SIGN for the update of other sections of SIGN 116. Prevention of diabetes was not included in the remit of SIGN 116 and this would be a proposal for a new topic to SIGN.
	JM	Satisfactory.	Thank you
	AG	Looks fine.	Thank you
	MC	It would be good to see who proposed these questions and what their interests are.	The register of interests of the guideline development group will be published alongside the guideline.
	SMac	All questions answered based on evidence base.	Thank you
	JM	Satisfactory.	Thank you
Annex 1			
	AG	Looks fine	Thank you
	MC	It would be good to see who proposed these questions and what their interests are.	The register of interests of the guideline development group will be published alongside the guideline.
	SMac	All questions answered based on evidence base.	Thank you
	JM	Satisfactory	Thank you

Algorithm			
Invited reviewers			**Type of response and declared interests**
SB	Professor Stephen Bain	Professor of Medicine (Diabetes), Swansea University, Swansea	Individual response. Remuneration from consultancy - Professor Bain has been a senior clinical academic since 1993 and since that time reports having received honoraria, teaching and research sponsorship/grants from the following: Abbott, Astra-Zeneka, Boehringer Ingelheim, BMS, Cellnovo, Diartis, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-aventis, Schering-Plough, Servier & Takeda. He has also received funding for the development of educational programmes from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med & Medscape. Professor Bain is a partner in Glycosmedia which carries sponsorship declared on its website.
AB	Professor Anthony Barnett	Emeritus Professor of Medicine/Consultant Physician, University of Birmingham and Heart of England NHS Foundation Trust, Birmingham.	Individual response. Remuneration from consultancy - have received honoraria for lectures and advisory work from MSD, Novartis, Astra-Zeneca, Boehringer-Ingelheim, Janssen, Servier,Sanofi-Aventis, Eli Lilly and Novonordisk.
GB	Mrs Gillian Booth	Specialist Pharmacist – Diabetes and Endocrinology, Forth Valley Royal Hospital, Larbert	Individual response.
MF	Professor Miles Fisher	Consultant Physician, Glasgow Royal Infirmary, Glasgow	Individual response. Remuneration from consultancy – advisory work for manufacturers of all diabetes therapies.
FG	Dr Fraser Gibb	Consultant Physician, Edinburgh Centre for Endocrinology & Diabetes, Edinburgh	Individual response.
SJ	Dr Scott Jamieson	General Practitioner, Kirriemuir Medical Practice, Kirriemuir. (GP representative for SIGN	Individual response.

		Council).	
BK	Dr Brian Kennon	Consultant Physician, Queen Elizabeth University Hospital, Glasgow	Individual response. Remuneration from consultancy – I have received speaker fees for providing non-pharmaceutical presentations for Novo-Nordisk and Lilly.
JMcK	Professor John McKnight	Consultant Physician, Western General Hospital, Edinburgh	Individual response. Non-personal support from commercial healthcare companies - I lead some of the commercial research in NHS Lothian that provides information about, in particular cardiovascular outcomes on different therapies. We have taken part in some of the studies now published.
SMac	Professor Sandra MacRury	Consultant Diabetologist, Raigmore Hospital, Inverness	Individual response.
SMcF	Mrs Susan McFarlane	Pharmacist Prescriber, Craigshill Health Centre, Livingston	Remuneration from employment - Boots employee providing clinical services based on endocrinology to GP practice in Livingston. Lothian Health Board employee providing clinical services on polypharmacy review, drug information, prescribing indicators to GP practice in Livingston. Pharmacy Champion for Lothian Health Board working with Chemist contractors across West Lothian. Remuneration from self employment – NES pharmacy peer review on consultation skills.
EP	Professor Ewan Pearson	Professor of Diabetic Medicine, University of Dundee, Dundee	Remuneration from consultancy - Personal Non-specfic. In the last 2 years I have received honoraria for speaking at scientific meetings from Lilly, Novo Nordisk, Astra Zeneca, MSD.
Open consultation			**Type of response and declared interests**
AZ		AstraZeneca	Group/Organisation response (Timo Riiali, Pricing and Market Access Manager). Nature of organisation – Pharmaceutical manufacturer.

			How might statements/ recommendations impact on your organisation? – AstraZeneca agrees that the SIGN guideline should be aimed at giving type 2 diabetes patients in Scotland timely treatment with the right medicines to minimise the risk of complications arising from the condition. Given all of AstraZeneca diabetes medicines belong to classes of medicines viewed as standard of care in Scotland, which are already incorporated into the SIGN 116 guideline, we do not believe the update will significantly increase or decrease company performance assuming our additional comments are sufficiently incorporated.
DC	Dr David Carty	Consultant, Glasgow Royal Infirmary, Glasgow	Individual response. Remuneration from consultancy – I have spoken at GP meetings and received financial remuneration from AZ, BI & Janssen.
SMC		Scottish Medicines Consortium	Group/Organisation response (Christine Hepburn, Principal Pharmaceutical analyst. Nature of organisation – health technology assessment. How might statements/ recommendations impact on your organisation? – SIGN guideline and SMC advice should be aligned.
MSD		Merck, Sharp & Dohme	Group/Organisation response (Basola Sowemimo, Health Economist). Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.

PSIG		Pharmacy Specialist Interests Group: Diabetes for RPS	Group/Organisation response (Sheila Tennant, Prescribing Lead Glasgow City HSCP). Nature of organisation – Professional body for pharmacists in Scotland. How might statements/ recommendations impact on your organisation? – SIGN guidance will inform prescribing practice and expenditure in primary care.
BI		Boehringer Ingelheim & Eli Lilly Alliance	Group/Organisation response (Michael Busse, Diabetes Medical Lead). Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – The draft SIGN guidelines, through helping clinicians prescribe the right medication for the right patient at the right time, will likely benefit the organisation.
GJ	Dr Gregory Jones	Consultant, Gartnavel Hospital, Glasgow	Individual response. Remuneration from consultancy – I have received speaker fees and advisory board payments from all diabetes drug manufacturers.
EL		Eli Lilly & Company Ltd (Lilly UK)	Group/Organisation response (Debby Nott, Health Economics Team Leader). Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – The draft SIGN recommendation in favour of/against Lilly products would promote/reduce uptake in NHSScotland which may increase/decrease company performance.
JN		Janssen Pharmaceuticals & NAPP Pharmaceuticals	Group/Organisation response (Debra Melhirst, Senior Scientific Advisor, Napp)

			Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – Our organisation would be weakened following a recommendation against canagliflozin as it would reduce uptake in NHS Scotland which may decrease company performance and would also decrease management options for patients in Scotland.
NN		Novo Nordisk	Group/Organisation response (Catherine Brant, External Relations Manager). Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – SIGN guidelines are well regarded within the UK and internationally and therefore we would anticipate an impact from any recommendations regarding Novo Nordisk medications.
RCPath		Royal College of Pathologists	Group/Organisation response (Dr Ellie Dow, Consultant in Biochemical Medicine). Nature of organisation – Professional body. How might statements/ recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation.
RCPE		Royal College of Physicians, Edinburgh	Group/Organisation response (Dr Stuart Ritchie, Consultant Physician). Nature of organisation – Professional body of Physicians. How might statements/ recommendations impact on your

			organisation? – No conflict of interest, with no material loss or gain associated with the outcome of this.
Sa		Sanofi	Group/Organisation response (Charles Jenkins, Value & Access Manager. Nature of organisation – Pharmaceutical Manufacturer. How might statements/ recommendations impact on your organisation? - The draft SIGN recommendation in favour of analogue insulin would enable uptake in NHS Scotland which may affect company Performance.
ABPIS		ABPI Scotland	Group/Organisation response (Keith Small, Policy & Public Affairs Manager). Nature of organisation – ABPI Scotland represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in Scotland and across the UK. Our industry, a major contributor to the economy of Scotland, brings life-saving and life-enhancing medicines to patients. We represent companies supplying more than 80 per cent of all branded medicines used by NHSScotland, and are researching and developing the majority of the current medicines pipeline, ensuring that Scotland and the UK remains at the forefront of helping patients prevent and overcome diseases. Globally, our industry is researching and developing more than 7,000 new medicines. The ABPI is recognised by the UK Government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation

			requirements including the pricing scheme for medicines in the UK. How might statements/ recommendations impact on your organisation? – Draft recommendations in this SIGN guideline will have no discernible impact on the function or productivity of our organisation. Our individual member companies may be affected.
Ta		Takeda UK Ltd	Group/Organisation response (Heena Howitt, Medical Manager). Nature of organisation – Pharmaceutical manufacturer. How might statements/ recommendations impact on your organisation? – The broader recommendation for the use of DPP-4 inhibitors after metformin (i.e. in dual and triple therapy or with insulin) to the previous SIGN guideline 116 may lead to increased DPP-4 inhibitor prescribing, which in turn may increase our company's performance.

	Comments received	Development group response
AB	Overall, this is well written and easy to understand. There are, however, several areas where I disagree or have some concerns:	Thank you for your comments.
	1. Target HbA1c up to and including the first intensification step should be 6.5% or individualised where this is inappropriate – provided such intensification does NOT include a sulphonylurea. Beyond this, I'm happy with target 7% or individualised/agreed with the patient. Clinical experience and research informs that if the lower target is aimed for then many more patients maintain HbA1c<7% by 3 years into the disease. Why wait for "failure"?	The glycaemic target is in keeping with the previous SIGN 116 publication. The original supporting evidence was not re-appraised by the current guideline development group as this was not part of this update.
	2. I am most concerned that sulphonylureas are listed as the only alternative to metformin as first-line therapy. These agents are associated with both hypoglycaemia and weight gain and may even have adverse cardiovascular effects. Why not give alternatives as DPP-4 inhibitors (weight neutral, virtually no risk of hypoglycaemia) or SGLT2 inhibitors (weight loss, virtually no risk of hypoglycaemia, cardioprotective - the latter now demonstrated with 2 different SGLT2 inhibitors!).	Noted. The treatment algorithm is for guidance. Other drug options are listed for use, and a note has been added that other drug classes are licensed for use as monotherapy when metformin and sulphonylureas are not tolerated. It should be noted that SMC have not approved any drug classes other than metformin or sulphonylureas for use in first-line therapy when such agents are appropriate. The guideline allows clinicians to tailor treatment according to the individual patient characteristics
	3. For second line agents I'm not sure why you give equal prominence to pioglitazone (associated with increased risk of weight gain, peripheral oedema, heart failure and fractures!). I'm also not clear why for SGLT2 inhibitors you say "certain agents" have shown cardiovascular benefits. Two of three agents from this class have now demonstrated CV benefit in hard endpoint trials suggesting this is a class effect. The use of these agents should be encouraged especially in patients with established CV disease particularly given their "efficacy package" which includes weight loss, low risk of hypoglycaemia and BP lowering. I think you should "downgrade" sulphonylureas and Pioglitazone and upgrade DPP-4 inhibitors and SGLT2 inhibitors for second line agents.	The algorithm and the written guidance allow clinicians a degree of flexibility to tailor glucose lowering treatment according to the benefits and risks of each agent or class of agents considered in relation to patient profile. The cited adverse effects of pioglitazone are clearly listed. As mentioned by the reviewer, the current evidence for CV benefit with SGLT2 inhibitors is limited to the two agents in which outcome trials have been completed, a situation which could change as further trials report. It is not our role to extrapolate beyond the current evidence. Prescribers are advised to refer to page 26 of the written guidance guideline/algorithm.
	4. You state that if intensification of basal insulin is required (4th line) then either add prandial insulin or switch to twice daily mixed biphasic insulin. Whilst these approaches are necessary for some patients they also run the risk of increasing weight loss and hypoglycaemia. Clinical trials and clinical experience have shown that the alternative	In the consultation version of the algorithm, 4th line treatment does permits addition of any 3rd line agent, including a GLP-1 RA. We have now clarified that the intensification box mentioned is for insulin intensification only.

	approach of adding a GLP-1 RA to basal insulin is at least as efficacious but with much less risk of hypoglycaemia or weight gain. Why is this not included in the algorithm? In summary - unfortunately, this algorithm is significantly out of date regarding best practice management of Type 2 Diabetes and needs a rewrite. The HbA1c targets also need revisiting for the earlier intensification steps. In its present form, this algorithm has very significant deficiencies and may inhibit best clinical practice.	The HbA1c target in SIGN 116 was <7.0% as in the consultation version of the algorithm. The original supporting evidence was not formally re-appraised by the current guideline development group as this was not part of this update. However, we are not aware of any new high quality evidence that would support a change.
ABPI	ABPI Scotland commends the Guideline Development Group on an easy to follow diagram, and the fact that it recommends regular assessment of patient HbA1c targets. However, we believe that the positioning of sulfonylureas visually may imply this is actually for first-line use. ABPI Scotland notes that an alternative approach title is situated above the Sulfonylureas segment, and we believe the alternative approach in a bold font or different colour scheme would highlight more appropriately its use as a second-line option. Another option might be to have both metformin and sulfonylurea side-by-side with metformin on the left with the usual approach title box and Sulfonylureas on the right with the alternative approach title box and conditions. *First-line treatment* ABPI Scotland notes that the alternative approach (an SU) to the usual care is included. However there is no alternative option for patients who are intolerant to the usual care, or who are overweight, possess osmotic symptoms, have had a previous hypoglycaemic event or if they drive, work at heights or operate heavy machinery. We suggest that there needs to be greater clarity about options in these circumstances. *Sulfonylureas* Following on from the above point, we suggest that a key or index is included for prescribers. This would help ensure that prescribers are aware of high risk groups for SUs, such as patients with renal impairment or those who are at increased risk of hypoglycaemia, as well as a small reminder to review the DVLA guidance document for drivers. *SGLT2s* We note that there is no mention of the *NICE*	Thank you. Thank you for this comment. This was not an intended implication and we have revised the layout accordingly. Agreed. Where 1st line therapy is contraindicated, other options are available as shown in second line. This has been clarified in the guideline. This information is included in section 12.1 (revised numbering) (Provision of Information) of the guideline. The technology appraisal that underpinned this NICE publication is

	(Multiple) Technological Appraisal Guidance No 390 (canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes) which has been endorsed by Healthcare Improvement Scotland. *GLP1s* There is no advice on combining GLP1s with SGLT2s as there is with the other classes. The addition of advice here would strengthen the guideline.	included as reference 82 in the consultation draft guideline. The MTA will be noted in the implementation section of the final guideline. Insufficient evidence on combining GLP-1s with SGLT2 inhibitors was identified to support any recommendation.
AZ	See separate submission	
SB	Overall, a well thought-out document. Why focus on CKD3A, since the comments equally apply to CKD stage 3 throughout the algorithm? Is acarbose available in Scotland? *Targets* The initial glycaemic target is set at <7% but the diagnostic level for type 2 diabetes is 6.5%. This implies that metformin treatment following diagnosis would be the exception rather than the norm - this seems out of step with USA/EASD and NICE guidelines. *1st line section* It seems odd to have the 'alternative approach' (sulphonylurea) at the top right of a guideline (where one would expect to find the default treatment). *2nd line section* Efficacy: DPP-4 inhibitors are generally less effective at lowering HbA1c than both Pioglitazone and SGLT2-inhibitors (all are termed 'moderate'). Main adverse events: Bladder cancer is still not proven for Pio. Saxa and alogliptin have heart failure warnings Fractures and amputation for canagliflozin In CKD: For consistency, in the DPP-4 section, why not have 'reduce dose (specific agents)'?	Thank you. There are small differences in regulatory guidance for some agents in CKD 3A *v* 3B. Moreover, we do not wish to imply that prescribing can be undertaken in primary care using a simple algorithm for patients with an eGFR <45 ml/min/1.73 m^2 who should be seen in secondary or tertiary care. Yes it is but is rarely used at present. It was included in an earlier draft of the guideline but was removed following consultation. The HbA1c target in SIGN 116 was <7.0% as in the consultation version of the algorithm. The original supporting evidence was not formally re-appraised by the current guideline development group as this was not part of this update. However, we are not aware of any new high-quality evidence that would support a change. Thank you for this comment. This was not an intended implication and we have revised the layout accordingly. Agreed: the efficacy descriptor for DPP-4 inhibitors has been changed to low/moderate.. Noted. We state in the top right hand column that "Prescribers should refer to the British National Formulary (www.medicinescomplete.com) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidance on licensed indications, full contraindications and monitoring requirements."

		The guidance on adverse events is intended to summarise those that are most clinically relevant according to current evidence.
	3rd line section I support the BMI cut-off for GLP-1RA which is lower than that in NICE NG28.	Thank you - this is unchanged from SIGN 116.
	I wouldn't agree that basal insulin has the 'highest efficacy'; several studies show a better HbA1c response with GLP-1RAs compared with basal insulin.	Thank you. We have changed “highest” to “high”.
	Sulphonylurea wouldn't always be withheld in basal insulin-treated patients.	Thank you. This has been revised to “consider stopping or reducing” sulphonylureas when used in combination with insulin.
	In CKD: For consistency, in the GLP-1RA section, why not have 'reduce dose (specific agents)'? Exenatide as QW 'Bydureon' isn't indicated for use in patients with CKD stage 3 (assuming that this equates to a creatinine clearance of <50mL/min).	Information for exenatide is listed in notes at the side of the algorithm.
	There is no mention of combination of GLP1-RAs and insulin, either free-mixing or as fixed ratio combinations.	In the consultation version of the algorithm, 4th line treatment does permit "free-mixing" addition of any 3rd line agent, including a GLP-1 RA. Use of fixed-ratio GLP-1 RAs with insulin is mentioned in the main guideline but there is insufficient space in the algorithm.
GB	Algorithm is written in a recognised and easy to use format.	Thank you.
	Wording around DPP4 adverse reactions - few - others all state adverse effects and so some clarification required here.	As adverse effects are not common, listing any here would give them undue prominence. Some are mentioned in the main guidance.
	When initiating basal insulin once daily at night then usually the SU would not be discontinued routinely.	Thank you. This has been revised to “consider stopping or reducing” sulphonylureas when used in combination with insulin.
	SGLT2 inhibitors - there should be a mention of the MHRA warning regarding lower limb ischaemia / risk amputation.	Agreed. This has been added.
	Spelling initiate under SGLT2 inhibitors in CKD3A.	Thank you. This typo has been corrected.
DC	At top I would suggest putting usual approach- metformin- on the left. As it stands the eye is drawn to the top left box which is gliclazide (alternative approach)	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.

	I don't think the efficacy of DPP4 and SGLT2 are the same (both say moderate) - is there scope to say that efficacy of SGLT2 high, or DPP4 low / moderate?	Agreed: the efficacy descriptor for DPP-4 inhibitors has been changed to low/moderate.
EL	Lilly UK welcomes the clear guidance on HbA1c treatment level decisions in order to expedite people through the treatment algorithm to improve outcomes for people with type 2 diabetes.	Thank you.
MF	This contains too much information. The algorithm from the previous SIGN guideline was excellent and contained much less information. The current algorithm could be simplified by sticking to the drug class name and having all of the other information re efficacy, side effects, etc in a table. Smaller point - should have metformin top left and SUs to the right as the eye will go top left first. Final point which I think is not fully covered in the guideline and algorithm is to highlight the two important new things since last guideline - new drug class in SGLT2 inhibitors, and new evidence for CV benefit. This could be in the introduction, the guideline, or the algorithm.	The algorithm tries to strike a balance between simplicity and being sufficiently informative to provide ready support for primary care prescribing. Few other responses to the consultation have made this point. Agreed: we have switched the positions of metformin and sulphonylureas. CV trials for GLP-1 RA are covered in Section 8.3 and for SGLT2 inhibitors in Section 9.3. The introduction summarises the rationale for updating the guideline and highlight the new developments, and there is a table in section 1.2.2 which elaborates on the sections with new and updated information.
FG	Is there an evidence base to suggest SU better in normal weight individuals - I don't think there is but there is evidence that metformin is equally effective in normal weight individuals. Refs: Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of obesity on glycaemic response to metformin or sulphonylureas in Type 2 diabetes. Diabet Med. 2006 Feb;23(2):128-33 Ji L, Li H, Guo X, Li Y, Hu R, Zhu Z. Impact of baseline BMI on glycemic control and weight change with metformin monotherapy in Chinese type 2 diabetes patients: phase IV open-label trial. PLoS One. 2013;8(2) My main criticism of this algorithm is that it is not sufficiently bold in the face of compelling evidence of cardiovascular and mortality benefit with SGLT2 inhibitors and, to a lesser extent, GLP-1 analogues. RCT evidence with SGLT2i is now backed up by real-world data. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis, The Lancet Diabetes & Endocrinology, 2017, ISSN 2213-8587, http://dx.doi.org/10.1016/S2213-8587(17)30258-9. (http://www.sciencedirect.com/science/article/pii/S2213858717302589) I think this algorithm should direct clinicians to use	Noted. We have revised this text to remove reference to weight. For each class of agents, the algorithm contains a comment on "CV benefit": for GLP-1s and SGLT2 inhibitors we have stated "Yes (specific agents)": we believe that this is the best summary of the current state of evidence possible within the space. The relevant CV outcome trials are discussed in the main guidance (GLP-1 in Section 8.3; SGLT2 inhibitors in Section 9.3). The recommendations in the main

	SGLT2i as second line after metformin in those with EXISTING CVD. Where contraindicated, not tolerated or ineffective, GLP-1 analogue should be the next recommended treatment in people with CVD. Is the risk of bladder cancer sufficiently high as to warrant inclusion in the algorithm with respect to TZDs? GLP-1 agonist - it is not appropriate to recommend SU dose reduction for all patients (e.g. HbA1c of 80 at commencement) Is there an evidence base to support stopping SU when initiating once daily insulin?	guideline have been revised to include the specific populations that derived cardiovascular benefit from SGLT2 inhibitors and GLP-1 agonists in the CV outcome trials. The algorithm advises that agents should be chosen according to patient profile. Thank you. It is included in the SPC and warnings published by MHRA. This has been revised. Noted. On consideration, we have made this guidance conditional in the revised algorithm. Thank you. This has been revised to "consider stopping or reducing" sulphonylureas when used in combination with insulin.
BI	To enable clinicians to clearly see which agent has cardiovascular benefit, we suggest modifying note 3 to the following: 3. CV outcome trial: Canagliflozin (published), Empagliflozin (published and within licence).	We have changed the note to refer the reader to the written evidence within the guideline. The licensing of individual agents is likely to change during the lifetime of the guideline.
JN	Janssen and Napp appreciate the opportunity to consult on the algorithm of the draft type 2 diabetes guidelines. Please see below our detailed comments. *1st line therapy* At present the 1st line section of the algorithm currently creates the impression that sulphonylureas (SUs) should be used first and then patients should move to metformin as the alternative approach. Although it does state 'alternative approach' for SU and 'usual approach' for metformin, the formatting of this section makes you want to read from left to right, so healthcare professionals (HCPs) may mistakenly think SUs should be the first option. Janssen and Napp would request that the boxes for metformin and SU be switched around so metformin is on the left hand side rather than SUs. *2nd line therapy* • Rather than stating 'add to metformin (and/or SU) one of:', Janssen/Napp request that this be amended to 'add to 1st line agent'. • At first line patients will only be on either metformin or an SU. They will not be on both as otherwise they are at 2nd line intensification. If HCPs are to add another agent to metformin and SU, these patients will be at 3rd line, not 2nd line of the algorithm.	Thank you. Thank you for this comment. This was not an intended implication and we have revised the layout accordingly. Noted. This has been simplified to "add one of." Whether an individual patient is at "first" or "second" line is, to some extent, a technicality as all second-line agents have indications for use as monotherapy when first-line drugs are not appropriate.

	Also by including this statement, it reads that if patients are on metformin and an SU, another SU can be added to patients' therapies. Therefore, by amending the statement to 'add to first line agent' this avoids any confusion for HCPs.	
	• Janssen/Napp request that 'or' be inserted after each of the drug classes so that it reads 'sulphonylurea or, pioglitazone or, DPP-4 inhibitor or, SGLT2 inhibitors. You have included this on the 3rd line section of the algorithm and this phrasing would also be useful here, as HCPs may think they need to start on the left hand side with SUs and then progress through the drug classes.	Noted this has been amended.
	• The algorithm currently states there is a probable CV benefit for pioglitazone. Janssen/Napp request that a reference(s) be added for this as currently none are available.	We disagree. The PROACTIVE trial is referenced in Section 6.1.3. Pioglitazone reduced major adverse cardiovascular outcomes pre-specified as a secondary outcome.
	• Moderate efficacy has currently been assigned to SGLT2 inhibitors. Janssen/Napp request that an asterisk be inserted next to moderate and a note added highlighting that canagliflozin 300mg has high efficacy, rather than moderate, based on available data (see references below).	There is insufficient space to cover each dose of each agent. This is covered in Section 9.1 of the full guideline.
	• The CV benefit for SGLT2 inhibitors is currently 'yes (specific agents)'. Janssen/Napp request that either in this box or in the note section for citation 3 that the specific agents empagliflozin and canagliflozin are included so HCPs are aware within the algorithm which agents have the benefits. Zaccardi F et al. Diabetes Obes Metab 2016; 18(8): 783-794 Schroeder M et al. A network meta-analysis to assess options for treatment intensification for patients with type 2 diabetes inadequately controlled on dual therapy. Poster presented at the 51st Annual Meeting of the EASD, 14th-18th September 2015. Stockholm, Sweden	For each class of agents, the algorithm contains a comment on "CV benefit": for GLP-1s and SGLT2 inhibitors we have stated "Yes (specific agents)": we believe that this is the best summary of the current state of evidence possible within the space. The relevant CV outcome trials are discussed in the main guidance (GLP-1 in Section 8.3; SGLT2 inhibitors in Section 9.3).
	3rd line therapy • Janssen/Napp recommend that the text 'from another class' should be added after 'add either an additional agent' to make it clear to HCPs that they should not be initiating numerous medications from the same class.	Thank you: this has been amended.
	• The algorithm needs to make it clear that dapagliflozin cannot be used in combination with pioglitazone.	This has been added to the "Notes."
	• Janssen/Napp recommend that 'can continue with SGLT2 inhibitors' be inserted in the GLP-1 agonist box as the licences for all SGLT2 inhibitors do not include any restrictions.	Thank you: this has been amended.

	Notes • Note 3 states 'see references (xx) and (yy). Can you please confirm what these references will be? • Note 8 refers to driving, occupational hazards, risk of falls and previous history with basal insulin. However, Janssen/Napp also recommend that such a note be included for SUs. *Other* • Will you now be including details from the CANVAS trial within this guideline? If so could you please provide this section of the guideline for consultation? • Napp/Janssen request that it is clear within the algorithm that at every line of intensification the SU dose needs to be reviewed in order to reduce the risk of hypoglycaemia, as this is not immediately clear.	This has been amended and now references page 26 of the main guideline. Note 8 *(now note 10)*: is to help prescribers choose the type of basal insulin. Information regarding the (lower) risk of hypoglycaemia with sulphonylureas is contained within the main guideline. Yes: see section 9.3 of the guideline. Unfortunately it will not be possible to consult on this aspect due to time pressures on publication. The algorithm makes it clear that the dose of every glucose-lowering agent should be considered at each stage.
SJ	I have a huge amount of concern about the top line 'set target for HBA1c <7%'. This target is not referenced. Indeed, there is no evidence at all that getting an HBA1c to <7% will be of benefit. Indeed as we now know to do so causes more harm and increases mortality. To state the whole premise of treatment of T2DM is to get HBA1c to <7% is missing the far bigger (and cheaper) issue to reduce glucose/carbohydrate intake of the patient. Rather than just move the ingested glucose around with drugs, why not just stop as much being ingested in the first place. Intensive use of medicines to reduce HBA1c does not prevent the organ complications of T2DM (http://bjgp.org/content/67/655/85) We cannot say we want anyone to have an HBA1c <7%.... we know this is harmful... I am concerned overall that this whole table just feels like prescribe, prescribe, prescribe to chase a target we know is not the whole picture. HBA1c chasing feels unidimensional and chasing at all costs carries huge risks, costs of these medications and harms - all for the sake of a target which we know will cause more deaths if we achieve it (ACCORD trial).	The HbA1c target in SIGN 116 was <7.0% as in the consultation version of the algorithm. The original supporting evidence was not re-appraised by the current guideline development group as this was not part of this update. However, we are not aware of any new high quality evidence that would support a change. The algorithm is for drug therapies used to help glucose lowering in people with type 2 diabetes. At every stage lifestyle measures are highlighted. More detailed guidance regarding lifestyle changes are included within Section 3 of SIGN 116 and were beyond the scope of this update. We disagree with these comments. The algorithm is a framework for prescribers to allow appropriate prescribing to allow individualised glucose targets to be reached. The full guideline states in section 3.6 that any glucose target "should be set for individuals in order to balance benefits with harms, in particular hypoglycaemia and weight gain".

	Realistic Medicine approach would suggest that chasing HBA1c as this algorithm is designed to suggest, misses a huge amount of as cost effective solutions which will improve so many other outcomes without the risks and costs of medications. Even the commonest drug metformin lacks evidence here with no placebo-controlled trial ever unambiguously showing reduced micro/macrovascular complications. With significant side effects. (Boussageon R, 2016) The decision to publish and push an agenda to prescribe more and more drugs overall feels very wrong when there is a lack of support and education to help patients reduce the intake. Have a GLP1 inhibitor for £100/month. For 10 patients it's £1000. Or for the same price pay for them to have a dietician and personal trainer. I know which I'd choose... Do we present our patients with realistic assessments of the lack of evidence and risks of the novel (and older) drugs here? Do we present our patients with all the risks of medications intended to be given lifelong and equally offer non-drug approaches?	We disagree - see UKPDS 34 as discussed in section 3 of the guideline. The algorithm is focused on drug therapies used to help glucose lowering in people with type 2 diabetes. At every stage lifestyle measures are highlighted. More detailed guidance regarding lifestyle changes are included within Section 3 of SIGN 116 and were beyond the scope of this update. We agree that healthcare professionals should ensure all treatment decisions are discussed fully with patients before they are implemented.
	If I worked for pharma I'd be really pleased with this table... as a GP I feel dishearten at the tiny box at the top which says 'lifestyle' - if only we put as much attention into reducing carb/glucose intake and increasing physiological consumption (AKA exercise) as we did to pedal drugs to move the glucose around after it is taken in.	Thank you for your opinion. No response required.
	Insulin was given patent free to drug companies in 1921... and yet for a drug almost 100 years old through tweaks and nudges it formulation it costs the NHS millions to remain a branded product - though it has changed minimally in that 100 year period. Drugs of a similar age oddly cost pennies...	Thank you for your opinion. No response required.
	I don't think despite all I've said I'll change the steam train towards what we are to publish here. That said, please consider NOT saying <7% as a target... we have no evidence for any target. The amount of harm which will come from chasing an HBA1c target <7% is potentially massive.	Thank you for your opinion. See above.
	We must consider what we want to achieve in treatment of T2DM. A target of <7% isn't the single surrogate we need. Please re-phrase this to reflect something of this sentiment. Refs: Boussageon R. Metformin as first line treatment for type 2 diabetes: are we sure? BMJ 2016; 352: h6748.	Thank you for your opinion. See above.

	Boussageon R. Prevention of complications in type 2 diabetes: Is drug glucose control evidence based? BJGP 2017; 67(655):85-87. Blonde L, et al. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin 2004 Apr;20(4):565-72	
GJ	The guideline is generally good. I think that the placement of the "alternative approach" sulphonylurea box is odd. It would make more sense that this was in the line below as with other second line approaches	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.
BK	I think overall this is a useful pragmatic approach that attempts to address a fairly complex issue and a significant amount of information so well done to the authors for summarising this challenging area. These are a few observations/suggestions:	Thank you.
	1. The way it is presented makes it look as if Gliclazide is the preferred agent even although I appreciate it does say alternative. As it is the first thing you read after '1st line agent' this may be misleading. May be worth swapping Metformin and Gliclazide around.....	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.
	2. In the CV benefit part for both SGLT2 and GLP-1 it clearly states 'specific agent'. I think in the interests of making this easier to interpret for non-specialists I think it should state at least somewhere in the algorithm (maybe on the additional text what those specific agents are namely Empa and liragluatide accepting there may have to be a disclaimer 'as per the time of going to print').	For each class of agents, the algorithm contains a comment on "CV benefit": for GLP-1s and SGLT2 inhibitors we have stated "Yes (specific agents)": we believe that this is the best summary of the current (constantly changing) state of evidence possible within the space. The relevant CV outcome trials and named agents are discussed in the main guidance (GLP-1 in Section 8.3; SGLT2 inhibitors in Section 9.3). We have referred prescribers to the appropriate pages in the guideline for discussion of CV effects of both drug classes.
	3. In the basal insulin section I wonder if we should state that NPH isophane insulin should be used first line. Long acting analogues may be consider if there is are concerns about hypoglycaemia.	This is captured by the box that says "Use NPH (isophane) insulin - or longer-acting analogues according to the risk of hypoglycaemia."
	4. The additional text at the side makes it seem quite 'wordy'. If this could be accommodated elsewhere that would be useful. I assume however the feeling was this is needed and should remain part of the document.	Thank you. However, it is important to have the "caveats" on the same page or they are unlikely to be read.
SMac	The algorithm is generally clear and easy to follow and the colour coding useful as is the information relating to efficacy etc for individual agents.	Thank you. We have received feedback that the colours imply too much preference for one agent over another so have removed some of the colour coding. Colour has been retained to highlight the “usual” and “alternative”

		approaches.
	The following additional comments/suggestions are offered:	
	Suggest Glycaemic targets and any reference to HbA1c levels should be expressed as mmol/mol with (%)	As this is a selective update, references to HbA1c will match the previous format of % with mmol/mol in brackets.
	The order of first line treatment seems inappropriate having the alternative approach before the usual approach in order of appearance; suggest reverse this to have metformin first with sulphonylurea second. This would also align better with plan for managing suspected type 1 diabetes	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.
	Suggest if possibility of type 1 diabetes suspected then refer to specialist diabetes team and if severe symptoms present urgent telephone referral to secondary care for review and advice should be advocated	Agreed: this advice has been inserted.
	There needs to be a note to remind prescribers to stop or not start metformin if eGFR is <30ml/min; while this may be in the text of the guideline, many clinicians will use the algorithm first and foremost	Renal guidance for CKD Stage 3A is included in the algorithm for all drug classes. Prescribers are asked to refer to the BNF before prescribing any agent.
	Injectable therapy should have equal place in third line therapy so suggest additional box next to SGLT2 inhibitor for injectable agent and follow with options as outlined depending on BMI	Moving to injectable therapy is a significant step for people with diabetes. The guideline group feels that it is justified to “group” the oral and injectable therapies in this way.
SMcF	Algorithm looks effective. Colour is a must to differentiate different stages of treatment. However difficulty seeing the numbers that the "notes " refer too, could these be done larger and in a different colour?	Thank you. Due to feedback after the open consultation we have decided to remove some of the colours. We will leave colours to differentiate the “usual” and “alternative” approaches. These have been increased in size.
JMcK	My main comment on the algorithm is some surprise that the DPP4s are second line and GLP1 therapy third line when the GLP1s are more effective to reduce glucose and prevent cardiovascular events.	SMC has restricted GLP-1 RAs for triple therapy in patients with inadequate glycaemic control on two oral glucose-lowering medicines.
	I'd put DPP4s as third line for patients who need a little boost to improve control, trying to avoid injection therapy but not a very effective option. Need to consider what we are trying to achieve with these drugs.	The algorithm allows for DPP-4 inhibitors to be used as 3rd line therapy.
	Is bladder Ca still considered an issue with pioglitazone? I thought the risk was very small if any? Should you clarify the actual risk?	The prominence of this potential safety issue has been downgraded following consultation.

	Is the CV risk data for empagliflozin stronger than the metformin data (UKPDS). If so why is metformin still first line?	The UKPDS and EMPA REG recruited very different patient populations (new diagnosis v established type 2 diabetes with high CVD risk and duration of diabetes of 12.8 years): the algorithm retains metformin first line.
	What is the significance of the CV risk reduction in each group of drugs? Can this be expressed in comparable terms? If it can be then what is the comparison for CV risk reduction of metformin, SGLT2 and GLP1 therapies. This might inform the order of use for these drugs.	The algorithm can provide only a telegraphic guide. The guideline text contains more detail and the relevant references. See also above comments.
MSD	MSD commends the Guideline Development Group (GDG) on a succinct algorithm. There are a few areas we feel input might further improve interpretation of the algorithm.	Thank you.
	Treatment Flow MSD commends the GDG on an easy to follow flow diagram. However, we believe that the positioning of SUs visually may imply this is in fact first line use. MSD notes that an alternative approach title is above the SU segment, we believe the alternative approach in a bold font or different colour scheme would highlight more appropriately its use as a second option. Another option might be to have both metformin and sulfonylurea side-by-side with metformin on the left with the usual approach title box and SU on the right with the alternative approach title box and conditions.	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.
	The box for SUs in second line says “See above” in reference to the information earlier. For clarity we feel including the information in this box as well lends itself visually to users to the guide, enabling comparison between the varieties of therapy agents to choose from.	Noted but it is felt that the algorithm is already very ‘busy’ and the empty space here is preferred.
	First Line Treatment Option MSD notes that usual care is metformin and the alternative approach is an SU (If intolerant to metformin and the patient is not overweight, or has osmotic symptoms); there is however no option if a patient is metformin intolerant and overweight/possesses osmotic symptoms, or indeed if they have had a previous hypoglycaemic event, or if they drive/work at heights/operate heavy machinery.	The algorithm has been altered so that prescribers are advised to go to second line more rapidly if first line therapies are not tolerated or inappropriate.
	For these sorts of patients it is our belief the use of a DPP-4 as monotherapy is usually recommended.	Thank you. The algorithm has been updated to include alternative first-line options where both metformin and sulphonylureas are not tolerated.
	Sulfonylureas (SUs) As a follow on to the point above, could the GDG	This information is included in Section

	kindly consider including a key for prescribers to be aware of high-risk groups for SUs, such as patients with renal impairment, and those who are at increased risk of hypoglycaemia as well as a small reminder to review the DVLA guidance document for drivers.	13.1 of the guideline (Provision of Information) but there is insufficient space to include it in the algorithm. .
	The efficacy of SUs has been designated HIGH by the GDG. Within the full guidance, no information has been given to detail the reduction in HbA1c by SUs. Whilst this figure is presented for DPP-4s and other treatments, the inability to make a direct comparison in the full guidance does not support this conclusion. Arjona ferreira et al.[1, 2] found that HbA1c reduction for SUs and DPP-4s were comparable. If there are no data proving this statement, we believe a parity placement of efficacy between SUs, DPP-4s and other treatments is appropriate.	While an absolute reduction in HbA1c for sulphonylureas has not been included in the guideline, it is noted that the AHRQ review found no significant difference in effect on HbA1c between sulphonylureas and metformin, and insufficient evidence to report on the difference with TZDs or DPP-4s as monotherapy. However, the same review also reported that metformin reduced HbA1c significantly more than DPP-4s, so on balance we have not suggested that all classes of drug have identical glucose-lowering effect but have suggested an informal hierarchy of categories. The AHRQ review which we have cited as evidence includes one RCT by Arjona-Ferreira but deems the evidence base insufficient to form a conclusion.
	Second and Third Line Treatment Intensification SGLT2s are positioned as options at both the second and third treatment stage, but may not be appropriate for a significant number of patients: i.e. patients with an eGFR <60. We currently estimate that around 27% of diabetes patients have moderate-to-severe renal impairment[3]. We believe the algorithm should clarify which patient cohorts 'are' and 'are not' appropriate for certain medications; Perhaps an addendum containing the various therapeutic agents which are either suitable or unsuitable in renal impairment could be added.	The algorithm already highlights that SGLT2 inhibitors should not be initiated in people with CKD Stage 3A.
	We also suggest the SMC guidance and restrictions on the various DPP-4 inhibitor agents be highlighted in the algorithm to further improve decision making. For instance, saxagliptin is confined for use as a combination with insulin (with or without metformin) and alogliptin is approved for use as a dual therapy alone. This information would allow prescribers to better select therapeutic choice depending on patient intensification.	The algorithm clearly refers prescribers to the SMC for more granular advice.
	DPP-4s MSD notes that a key has been made regarding dose reduction of linagliptin in CKD stage 3 but no note on cardiovascular differentiation in DPP-4 agents. We feel that further emphasis should be made on the non-interchangeability in this class	Cardiovascular data for the different DPP-4 agents are discussed in the main guideline text.

	with regards to cardiovascular morbidity. According to the full guideline, saxagliptin and alogliptin had an increase in rate of hospitalisation for heart failure whereas with sitagliptin results were almost identical to placebo. Considering the risk of cardiovascular disease in this patient group, a key highlighting this would be better for helpful. We also suggest the inclusion of a key to indicate there are SMC restrictions to various DPP4 agents and prescribers should be aware of these when making therapeutic choices. *SGLT2s* According to the MHRA, canagliflozin may increase the risk of lower-limb amputation (mainly in the toes) in type 2 diabetes patients[4]. MSD feels the risk of toe amputation should be highlighted within the algorithm. As vigilant foot care is important for all patients with diabetes, MSD feels highlighting this will serve as a reminder to prescribers when prescribing canagliflozin on the foot risk status of patients as well as the risks posed by certain therapeutic agents. This will keep consistency in the structure of warning for specific agents as was done for linagliptin in CKD stage 3. We would also recommend that the algorithm reflect that in accordance to SMC restriction, dapagliflozin and empagliflozin may be used as a dual therapy in combination with metformin only when a sulfonylurea is inappropriate[5, 6]. References 1. Arjona ferreira JC et al. Efficacy and Safety of Sitagliptin Versus Glipizide in PatientsWith Type 2 Diabetes and Moderate-to-Severe Chronic Renal Insufficiency. Diabetes Care. 2013 36:1067–1073 2. Arjona ferreira JC et al. Efficacy and Safety of Sitagliptin in Patients With Type 2 Diabetes and ESRD Receiving Dialysis: A 54-Week Randomized Trial. Am J Kidney Dis. 2013;61(4):579-587 3. Middleton RJ et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant. 2006;21(1):88-92 4. MHRA (March 2017). SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes), GOV.UK, available at https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-increased-risk-of-lower-limb-amputation-mainly-toes?UNLID=299204794201752215141 2 (accessed 14 August 2017) 5. SMC No. 799/12 available at: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/799_12_dapagliflozin_Forxiga/dapagliflozin_Forxiga_2nd_Resub (available 14 August 2017)	Cardiovascular data for the different DPP-4 agents are discussed in the main guideline text. The algorithm clearly refers prescribers to the SMC. Now that the CANVAS trial is published, this is included in the full guideline text. The algorithm now advises prescribers to check MHRA safety warnings. The algorithm advises prescribers to refer to the BNF and SMC before prescribing.

	6. SMC No. 993/14 available at: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/993_14_empagliflozin_Jardiance/empagliflozin_Jardiance (accessed 14 August 2017)	
NN	Thank you for the opportunity to review and provide feedback into the SIGN diabetes algorithm. Reassuringly this appears to be the first national UK algorithm to take a multifactorial approach in guiding clinicians to choose the most appropriate treatment and this is a very important and positive step. SIGN guidelines are recognised within Scotland, across the UK and internationally as a valuable clinical reference. The balance between evidence and providing options for individualised patient care will be welcomed by clinicians. The final algorithm helpfully references the benefits (and disadvantages) of individual medications on patient factors to aid clinical decision-making. It therefore seems inconsistent to recognise the importance of evidence-based practice, and the individualised approach but then to limit the patient choices for care by placing GLP-1RA's as a third-line option, the class of medication which arguably best fulfils the multifactorial criteria. As a stated clinical guideline, the decision to commence a drug should be guided by patient and drug profiles and should not be influenced or determined by cost or resource use. In an environment where there are numerous other formulary and cost based algorithms, this clinical algorithm should empower clinicians to choose a GLP-1RA as a second-line therapy for the appropriate patient. Given that cardiovascular disease is the main cause of death in patients with type 2 diabetes, inclusion of therapies with proven benefits to reduce cardiovascular mortality and morbidity will be evidence based and supportive of patient centric choices. A third-line agent would mean at best, 12 to 18 months after two or three agents have failed, and this is if regular reviews and actions are undertaken. An earlier option for individual patients will lead to better outcomes (glycaemia, cardiovascular, weight and hypoglycaemia). Furthermore, regulatory bodies have recognised the cardiovascular benefits seen in the LEADER trial and have updated the indication of Victoza® from treatment just of glycaemic control to treatment of diabetes, recognising the benefit of Victoza® on both glycaemia and cardiovascular events[1]. To date this is the only licenced GLP-1RA with this indication. In addition to guiding clinicians to think about the	Thank you. Thank you. SMC has restricted GLP-1 RAs for triple therapy in patients with inadequate glycaemic control on two oral glucose-lowering medicines. The average duration of diabetes in LEADER was 12.8 years SMC has restricted GLP-1 RAs for triple therapy in patients with inadequate glycaemic control on two oral glucose-lowering medicines.

	importance of managing cardiovascular risk when making treatment decisions, the algorithm clearly demonstrates the importance of considering efficacy, hypoglycaemia risk, weight, adverse events and CKD but the same point regarding the late positioning decision is as strongly relevant here: GLP-1RA's are clearly drug leaders in addressing glycaemic control, reducing weight and hypoglycaemia risk and indeed liraglutide can now be used in patients with severe CKD[1]. With clear clinical reasons for use, we therefore believe that there is clear justification for inclusion of GLP-1RA's at second line.	
	For clarity and ease of explanation, we have incorporated our suggestions in an amended algorithm. As stated at the beginning, we applaud the objectives of this algorithm to encourage clinicians to really focus on individual patient factors when making decisions about their care and we hope that our suggestions help in further highlighting those important areas. <u>The suggested amendments to the algorithm are highlighted below (see separate algorithm):</u>	Thank you.
	GLP-1RA's are placed alongside SGLT2 inhibitors as a second-line choice to enable clinicians to choose the most appropriate option, taking into account the individual clinical factors. We have explained above why we feel strongly that patients should have access to this.	SMC has restricted GLP-1 RAs for triple therapy in patients with inadequate glycaemic control on two oral glucose-lowering medicines.
	To enhance the clarity of the algorithm which encourages clinicians to consider the individual patient factors, we suggest adjusting the colouring of the table so that it more clearly focuses on consideration of patient and drug profile rather than highlighting the individual treatments.	In response to feedback to the consultation we have decided to remove many of the colours other than those covering "usual" versus "alternative" approaches.
	Given that this algorithm is often printed and used as a quick reference we think it is important to name the individual drugs with proven cardiovascular benefit rather than referring the reader to a reference which may not be readily available when viewing a printed version or a saved PDF of the algorithm; given that individual drugs are named elsewhere in the algorithm we assume this should not preclude the names being included here.	The algorithm is not a stand-alone document but a framework summarising the full guideline. The algorithm does direct prescribers to the relevant sections of the written guidance i.e. individual agents.
	We have added a simple outline to highlight within the notes section (along with the corresponding asterisks) that all medication should be reviewed at every step within the table. We have moved the information from the draft algorithm pertaining to GLP-1RA's to the notes	Drugs are only mentioned by name where they are the only ones used within that class.

	section. We assume that it is an unplanned omission that there is no mention of continuing a GLP-1RA along with basal insulin as this was clearly included in the draft guideline. It is indeed common clinical practice, within license and has demonstrated efficacy in clinical trials and real world evidence as a beneficial option for patients. We have therefore added this in the appropriate box.	At fourth line the algorithm states: " IF NOT REACHING TARGET AFTER 3−6 MONTHS, REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE ADD ADDITIONAL AGENT(S) FROM 3rd LINE OPTIONS (*NEED SPECIALIST INPUT*)." Read with the guideline text this important option is captured.
	Between the different classes of drugs in the second-line section, the word 'or' should be added as is the case in the third line section.	Thank you. The algorithm has been amended.
	Where the statement is 'ADD either an additional oral agent' under third line we suggest this should be amended to 'Add* either an additional oral agent from a different class' with an asterisk next to 'Add' reminding one should only continue medication if it is working. Whilst it might perhaps obvious to some, it is important to state the additional agent should be from a different class.	Thank you. The algorithm has been amended.
EP	I appreciate that this is an algorithm to be used as a guide for management of hyperglyceamia and as such cannot capture all eventualities. My comments in part address the algorithm, and in part the guidance.	The algorithm is intended to guide appropriate prescription of glucose lowering drugs, taking into account efficacy of glucose lowering, cardiovascular risk AND adverse effects, such as hypoglycaemia. It is not focused on a single outcome.
	1. Sulphonylurea use first line in those who are not overweight. This statement does not seem to be evidence based, and may stem from the fact that UKPDS used metformin in overweight and therefore only sulphonylureas or insulin were used in the non-overweight. In observational data from Scotland, supported by the PK of metformin, there is an inverse correlation between efficacy and BMI for metformin (i.e. metformin works better in slimmer people) PMID: 16433709 as such I do not think metformin should be reserved for overweight but should be used first line in everyone unless there is a C/I or intolerance. Ref: Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of obesity on glycaemic response to metformin or sulphonylureas in Type 2 diabetes. Diabet Med. 2006 Feb;23(2):128-33	Agreed: this has been rephrased and the reference to weight removed.
	2. Metformin, AKI and lactic acidosis. The issue of lactic acidosis in relation to metformin continues to be much debated. The meta-analysis described in the guidance is of RCTs and as such excludes patients with comorbidities. We have just published a paper using Tayside data showing that the odds of lactic acidosis in metformin users are increased two-fold relative to	We regard this as important but difficult to include in the algorithm: there are also implications for several other agents during acute illness. These issues are covered on in the Provision of Information section of the full guideline.

	non-metformin users; this is largely in the context of Acute Kidney Injury PMID: 28432751. This provides evidence supportive of the KDIGO guidelines that recommend stopping metformin in illnesses that predispose to AKI. This recommendation should be incorporated into the guideline and may merit a foot note in the algorithm.	
	3. Stopping rules if ineffective. I realise that I was partially for these stopping rules appearing in the last SIGN guidelines. Whilst I still maintain we should stop ineffective drugs, I have been struggling recently to define what is 'ineffective'. Unpublished data from the MRCABPI Mastermind consortium highlights how variable visit-to-visit HbA1c can be, this makes it hard to say that, for an individual, a reduction is a drug response or random variation (due to lifestyle factors). This makes it hard to 'protocolise' such a step. At this stage I would recommend avoiding the HbA1c value and timescale - e.g. say 'discontinue if drug ineffective', or 'discontinue if no sustained benefit over a number of repeat HbA1c measures'. I appreciate that will raise questions about how these are defined!	Noted. This was discussed by the GDG but the consensus was that there has to be some explicit guidance around stopping: so we have left the recommendation as it stands. We accept that, in practice, this should be interpreted with due attention to the individual patient's profile and characteristics, than a strict adherence to the numbers.
	4. Those with prior CVD. Whilst the guideline is focussing on hyperglycaemia reduction, the stepwise algorithm does not seem to take into account the recent studies showing CV benefit from SGLT2i and some GLP-1RAs. I think it would be beneficial in the algorithm to include a footnote that patients with prior CVD (or who are otherwise high CV risk) should be treated with SGLT2i and GLP-1RA in preference to other second or third line treatments. Also the CV benefit from SGLT2i was seen even in those with eGFR <50.	This is included in the written sections and updated recommendations for GLP-1 RA and SGLT2 inhibitors. The algorithm highlights drug classes with cardiovascular benefit and refers prescribers to the written guidance to see info on specific drugs. Positioning of the different drug classes is also determined by SMC guidance.
	5. Pioglitazone and insulin. Whilst this can be an effective combination it greatly increases the risk of oedema and heart failure. The algorithm suggests that insulin can be added to those on TZD at the point of insulin initiation - I would be cautious of this unless undertaken by a specialist. I would suggest a cautionary note (if previous good response to pioglitazone; caution increased risk of oedema and heart failure).	Noted. The algorithm highlights the risk of oedema with pioglitazone. The GDG is aware of evidence of fluid retention when pioglitazone is combined with insulin, but in an algorithm there is insufficient space to highlight this adverse effect further as it is already listed above.
	6. CANVAS has now reported. Presumably the guidelines can be updated to reflect this?	Yes: see section 9.3 of the guideline
PSIG	I liked the layout and thought it was helpful covering the benefits & ADEs. Good to see advice on stopping DPP4s and SUs with GLP1s & Insulin respectively.	Thank you
	A few comments below for consideration:	Thank you for this comment. This was

	1. Position of SU on the left hand side is confusing: suggest swapping position of metformin & SUs.	not an intended implication and we have revised accordingly.
	2. Compliance/concordance should be addressed at each step: "if not reaching target after 3-6 months... " review compliance	Agreed. This has been added – it was previously in SIGN 116. We have chosen to use the term “adherence”.
	3. "NPH insulin or longer-acting analogues according to risk of hypoglycaemia". This needs to reflect SMC statement on analogues which is not if "at risk of hypo" but if patient suffers recurrent episode of hypo or requires assistance with injection.	Noted, however space limits the ability to include a full description. The SMC advice relates to two factors influencing insulin choice. Further details are available in section 13.1 of the full guideline.
	SMC statement for Lantus: "In patients with type 2 diabetes it should be restricted to those who suffer from recurrent episodes of hypoglycemia or require assistance with their insulin injections."	Noted
	4. Would be helpful to add something about stopping treatment if minimum HbA1c target reduction not met within the first 3-6 months of treatment.	This already features in the algorithm.
	5. * continue medication at each stage if either individualised target achieved or HbA1c falls more than 0.5%. As a minimum the expectation is that treatment should reduce HbA1c by 0.5% is it not? This suggests a lower target reduction is acceptable.	Correct. Glucose targets are individualised and whilst it is anticipated we should aim for 0.5% reduction with most drugs, in some cases, dependant on the patient, a smaller reduction may be acceptable.
RCPE	This document will have significant use in routine clinical practice and therefore layout and ease of reading is crucial. If this is to be on a single page of A4 it is currently a very busy slide.	Noted. We have worked to reach the best compromise with maximum guidance requested by the clinical community while preserving clarity on one page.
	HbA1c is no longer having dual reporting, therefore recommend reporting only in mmol/mol as aligned to current good clinical practice.	Noted but many people with diabetes and healthcare professionals still refer to %. Having both allows everyone to follow the guidance.
	It is confusing to have the alternative 1st line treatment option to the left of the usual pathway, as the document would appear to read best from left to right, perhaps the long arrow from suspected type 1 to insulin could be removed and used as a textbox only to allow the switch.	Thank you for this comment. This was not an intended implication and we have revised the layout accordingly.
	GLP-1 therapy, has high efficacy, CV benefit, with low hypoglycaemia risk and weight loss – should it not be considered in 2nd line therapies as its effect profile is superior to some of the oral agents.	SMC has restricted GLP-1s for triple therapy in patients with inadequate glycaemic control on two oral anti-diabetic medicines.
	The re-enforcement of auditing effectiveness after 3-6 months is a real strength and it would be	Thank you.

	really advantageous to ensure this is clear.	
SMC	SMC has previously sent comments on the draft guideline on pharmacological treatment of diabetes. We have reviewed the draft algorithm as a stand-alone document, since the revised draft guideline is not available on the SIGN website. As a general comment, the algorithm is very "busy" compared with the previous one, which may make it less user-friendly. We note that GLP1-agonists are recommended for third-line use and this is in line with SMC advice and our previous feedback to SIGN on the draft guideline. Cardiovascular benefit of SGLT2-inhibitors and GLP1-agonists: Note that SMC has not reviewed the evidence regarding CV benefits of these medicines, since these did not involve a change to the licensed indication. The algorithm and guideline should ensure that information relating to CV benefit is consistent with the licence for these medicines.	Noted. We have worked to reach the best compromise with maximum guidance requested by the clinical community while preserving clarity on one page. Noted. It is acknowledged that this is a rapidly-changing situation.
Ta	Takeda UK Ltd. are generally supportive of the algorithm proposed for the draft guideline “pharmacological management of glycaemic control in people with type 2 diabetes”; the draft algorithm is reflective of the draft recommendations proposed within the guideline. Assuming the recommendations do not change, Takeda would be happy for the algorithm to be published without major change. As per our comments for the guideline consultation on 25 May 2017, given the substantial and rising proportion of the NHS Scotland budget spent on prescribing in diabetes, we recommend that SIGN include recommendations within the algorithm based specifically on cost impact (both between classes and within class of therapy) in order to encourage rational and cost-effective prescribing. Regarding the SGLT2 inhibitor class, it may be prudent to consider other key potential adverse events that have recently warranted licence changes and direct to healthcare professional communications (e.g. diabetic ketoacidosis, extremity amputations) so that the prescriber can make a robust risk:benefit evaluation before choosing a treatment option. We are supportive of the “probable CV benefit” detailed for pioglitazone, for which recent data	Thank you. Thank you. We refer to SMC guidance for budget impact. Prescribers are advised in the algorithm to refer to the BNF before prescribing any drug and to be aware of MHRA warnings. Thank you.

	further supports this notion. A pan European multi-database observational cohort study of pioglitazone evaluated the risk of mortality in patients with Type 2 diabetes and was recently published in the British Medical Journal Open Diabetes Research and Care. This was a planned secondary outcome in a study primarily assessing the association of pioglitazone use with bladder cancer risk. The study of 56,337 patients in both the pioglitazone exposed and non-exposed groups across four European countries reported that pioglitazone exposure was associated with a 33% statistically significant reduction in the risk of all-cause mortality (adjusted HR 0.67 [95% CI: 0.64-0.70]). Comparators included a full range of antidiabetic treatment regimen from metformin alone (11%) to insulin used alone or in combination (36%). Results should be interpreted with caution due to the potential for residual confounding. Strongman H, Korhonen, P, et al. Pioglitazone and Risk of Mortality in Patients with Type 2 Diabetes: Results from a European Multi-Database Cohort Study. British Medical Journal Open Diabetes Research and Care [online].http://drc.bmj.com/content/bmjdrc/5/1/e000364.full.pdf	
Sa	Section: *'3rd LINE'. GLP1 AGONIST.* This section states that GLP1 Agonists are suitable 'IF BMI ≥ 30 kg/m^{2}' However, based on the available evidence for lixisenatide the benefits are not exclusively for patients with a BMI greater than 30 kg/m^{2}. In Riddle et al, the mean ± SD BMI at baseline was 32.1 ± 6.2, with 40% of patients having BMI <30 and 60% of patients having BMI ≥30. In Riddle et al, the mean ± SD BMI at baseline was 31.8 ± 6.3, with 46.2% of patients having BMI <30 and 53.8% of patients having BMI ≥30. Section: *'BASAL INSULIN'* This section currently states: 'NPH (Isophane) insulin or longer-acting analogues according to risk of hypoglycaemia' We would suggest: 'NPH (Isophane) insulin or longer-acting analogues according to individual patient need.' REFERENCES: Reference 75 from draft guidance: Riddle MC, Forst T, Aronson R, Sauque-Reyna L, Souhami E, Silvestre L, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care 2013; 36 (9):2497-503	The BMI cut-off has been inherited from SIGN 116. We are not aware of new evidence to support a lowering of this threshold. The mean BMI in the referenced study was 32.1 kg/m^{2}. The same may be true for other GLP-1 RAs. Thank you but we wished to be more specific and have left this unchanged from SIGN 116.