NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Semaglutide for managing overweight and obesity [ID3850]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Semaglutide for managing overweight and obesity [ID3850]

Contents:

The following documents are made available to consultees and commentators:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Semaglutide for managing overweight and obesity [ID3850]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Professional group	Obesity Group of the British Dietetic Association	Section 1.1 Pg 3: These guidelines focus on reduced calorie intake and increased physical activity. NICE CG189 recommends multicomponent interventions i.e. inclusion of behaviour change alongside diet and activity. Multicomponent interventions are the treatment of choice. See recommendations 1.5.1 to 1.5.3 i.e. ensure weight management interventions include behaviour change interventions to increase physical activity or decrease calorie intake.	Thank you for your comment. The remit of this guidance is to appraise the clinical and cost effectiveness of semaglutide for managing overweight and obesity. The recommendation specifies that semaglutide should only be used with multidisciplinary management, however, further recommendations on the management of obesity cannot be made within this guidance.
2	Professional group	Obesity Group of the British Dietetic Association	Section 1.1 Pg 3: We are pleased that the recommendation to use lower BMI cut-off points for specific ethnic groups is explicitly acknowledged, in light of the increased risks to these groups.	Thank you for your comment.
3	Professional group	Obesity Group of the British Dietetic Association	Section 1.3 Pg 3: We have concerns about the recommendation to use semaglutide for only two years. In one sense this suggest that obesity is a short-term condition, which it is not. However, we also feel that this recommendation lacks clarity e.g. can semaglutide be used repeatedly and if so, what is the recommendation around that?	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only

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				available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years. Further information on retreatment with semaglutide has been included in section 3.14 of the FAD.
4	Professional group	Obesity Group of the British Dietetic Association	Pg. 4. In place of 'Reverses prediabetes' we suggest 'helps people with prediabetes achieve a normal blood glucose more frequently'.	Thank you for your comment. The Final Appraisal Document has been updated as suggested.
5	Professional group	Obesity Group of the British Dietetic Association	Pg 4: 'exceptionally with a BMI of 30-34.9kg/m^2'. There is a lack of clarity around what 'exceptionally' means in this context. Could specific examples be given for clarity?	Thank you for your comment. The term exceptionally has been removed from the recommendation. The recommendations have been clarified to refer to the specific criteria for semaglutide to be offered based on the criteria in NICE's clinical guideline on obesity: identification, assessment and management.
6	Professional group	Obesity Group of the British Dietetic Association	Section 2.1 Pg 4: Could this be amended to 'as an adjunct to multicomponent interventions to increase physical activity and reduce calorie intake'?	Thank you for your comment. The wording in section 2.1 reflects the indication as written in the summary of product characteristics. Therefore, this section has not been updated.
7	Professional	Obesity	Section 3.1 Pg 5: Obesity is recognised as a lifelong condition,	Thank you for your comment. The

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	group	Group of the British Dietetic Association	yet semaglutide is only recommended for a maximum of two years. There appears to be discrepancy here which is unexplained.	committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
8	Professional group	Obesity Group of the British Dietetic Association	Section 3.2 Pg 6: In relation to the statement that Tier 3 services are normally accessed for up to two years, we suggest that access to Tier 3 services (and the length of time they are accessed), is very variable, and 2 years is usual for Tier 2 services.	Thank you for your comment. The committee heard from clinical experts that tier 3 services are usually accessed for up to 2 years, although noted comments that services and length of time they are accessed is variable (see Final Appraisal Document section 3.2). The committee also understood that tier 2 services can be accessed for 12 weeks, which is based on Public Health England guidance for delivering and commissioning tier 2 adult

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				weight management services.
9	Professional group	Obesity Group of the British Dietetic Association	Section 3.3. Pg 7: We note that behavioural support was also offered within the STEP1 programme. We recommend that this is made explicit as an expectation of what would be part of the core offer of a care package.	Thank you for your comment. The committee recognised that it was appropriate for treatment with semaglutide to be given alongside management from a multidisciplinary team, which was reflective of the intervention in the STEP 1 clinical trial, which included behaviour change interventions (see Final Appraisal Document section 3.3).
10	Professional group	Obesity Group of the British Dietetic Association	Section 3.3 Pg 8: We agree that semaglutide should be offered alongside specialist weight management interventions. As per our earlier comment, we would like explicit mention of multicomponent interventions including behaviour change rather than a focus only on diet and physical activity, since behaviour change will be needed in both those areas.	Thank you for your comment. The committee recognised that it was appropriate for treatment with semaglutide to be given alongside management from a multidisciplinary team, which was reflective of the intervention in the STEP 1 clinical trial, which included behaviour change interventions (see Final Appraisal Document section 3.3).
11	Professional group	Obesity Group of the British Dietetic Association	Section 3.4 Pg 8: In relation to the population with a BMI of 30kg/m^2 and above, could we ask that (obese) in brackets is replaced with (obesity), since that is non-stigmatising language.	Thank you for your comment. This change has been made in the Final Appraisal Document section 3.4.
12	Professional group	Obesity Group of the British Dietetic Association	Section 3.4 Pg 9: In relation to 'Only exceptionally, referrals are made for people within this population, for example, when the person has a complex disease state or needs that cannot be managed adequately in tier 2', we agree with this but suggest that for clarity it is placed in the earlier recommendations.	Thank you for your comment. The recommendations refer to the specific criteria for semaglutide to be offered based on the criteria in NICE's clinical guideline on obesity: identification, assessment and management. It is not appropriate to only include the examples provided in section 3.4 of the Final Appraisal Document in the recommendation as these are not fully comprehensive.
13	Professional	Obesity	Section 3.4 Pg 10: 'The committee concluded that the	Thank you for your comment.

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	group	Group of the British Dietetic Association	appropriate population for semaglutide comprises people at the highest risk for the adverse effects of obesity, which is the population eligible for specialist weight management services': We agree with and welcome this statement.	
14	Professional group	Obesity Group of the British Dietetic Association	Section 3.6 Pg 11: In relation to STEP1, counselling is mentioned here for the first time. We would like this aspect highlighted elsewhere to ensure that those starting semaglutide are supported appropriately.	Thank you for your comment. The recommendations and committee discussion section of the Final Appraisal Document includes that semaglutide should only be used within a specialist weight management service which includes multidisciplinary management.
15	Professional group	Obesity Group of the British Dietetic Association	Section 3.6 Pg 12: 'The committee recognised that the highest risk population should be treated': We agree with and support this recommendation.	Thank you for your comment.
16	Professional group	Obesity Group of the British Dietetic Association	Section 3.11 Pg 16: We agree with and welcome this stop rule. We think it is clear and sensible.	Thank you for your comment. The recommendations have also been updated to include this stopping rule.
17	Professional group	Obesity Group of the British Dietetic Association	Section 3.12 Pg 16: 'and that there would be no retreatment': this is not included in the earlier guideline and we think it should be, for clarification. However, it is also not in line with the widespread recognition of obesity as a lifelong condition.	Thank you for your comment. The company's model included the assumption that there would be no retreatment with semaglutide, however the committee acknowledged that retreatment might be appropriate for some people if they were eligible for treatment again according to the same starting criteria (see the Final Appraisal Document [FAD] section 3.14). Section 3.14 has been added to the FAD for clarification around retreatment.
18	Professional group	Obesity Group of the British	Section 3.12 Pg 16: 'The clinical experts explained that some people who have regained weight after weight loss with semaglutide may wish to take it again'. We	Thank you for your comment. The committee acknowledged that retreatment might be appropriate for some people if

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		Dietetic Association	agree with this statement and would encourage this to be reconsidered. The impact of weight regain and potential feelings of failure are likely to be substantial in those living with overweight or obesity. This is of concern particularly given the risk of worse mental health in this group.	they were eligible for treatment again according to the same starting criteria, which would include rereferral to specialist weight management services (see the Final Appraisal Document [FAD] section 3.14).
19	Professional group	Obesity Group of the British Dietetic Association	Section 3.12 Pg 17: In relation to the 2 years of semaglutide treatment and the alignment with Tier 3 services, at least some Tier 3 services are commissioned only for one year. would patients accessing those services have to stop taking semagluide if they are discharged before 2 years?	Thank you for your comment. The committee noted that on average specialist weight management services are currently accessed for 2 years however also acknowledged that the length of time these services can be accessed may be shorter in different areas of the country (see Final Appraisal Document section 3.2). The recommendations specify that semaglutide should only be used within a specialist weight management service, therefore in some cases where specialist weight management is provided for less than 2 years, semaglutide treatment length may also be shorter than 2 years.
20	Professional group	Obesity Group of the British Dietetic Association	Section 3.13 Pg 17: In relation to the assumption that 'weight would be in line with what it would be in the average population after 5 years of only diet and exercise', we suggest that this negates the emotional impact of weight regain in those living with overweight or obesity.	Thank you for your comment. Section 3.13 of the Final Appraisal Document (FAD) describes the assumption included in the model around weight regain. The committee was aware that stopping treatment, which is associated with weight regain on average, may have a detrimental psychological impact (see FAD section 3.12). The committee concluded that average time to weight regain is an area of uncertainty.
21	Professional group	Obesity Group of the British Dietetic	Section 3.17 Pg 20: We disagree with the following recommendations, for reasons already outlined: • a maximum treatment duration of 2 years (see section 3.12)	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight

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		Association	no retreatment throughout the full time horizon of the model (see section 3.12)	management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years. The committee acknowledged that retreatment might be appropriate for some people if they were eligible for treatment again according to the same starting criteria, which would include rereferral to specialist weight management services (see the Final Appraisal Document [FAD] section 3.14).
22	Patient expert	Ken Clare	Has all of the relevant evidence been taken into account? Yes	Thank you for your comment.
23	Patient expert	Ken Clare	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes	Thank you for your comment.
24	Patient	Ken Clare	Are the recommendations sound and a suitable basis for	Thank you for your comment. The

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	expert		guidance to the NHS? Yes but some concerns about 2 year duration of treatment	committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
25	Patient expert	Beverley Burbridge	Semaglutide treatment is going to be limited for a treatment period of 2 years, this needs to be a lifelong treatment.	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like

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				obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
26	Patient expert	Beverley Burbridge	People that have had bariatric surgery and a start BMI of >40, surely the damage has been done to the heart so Semaglutide could be issued to people that have a current BMI of 27-30 as a maintenance dose. Many people find it difficult even after surgery to maintain.	Thank you for your comment. The committee agreed that it was appropriate to consider semaglutide for a population who were at the highest risk for the adverse effects of obesity and were likely to gain the most benefit from semaglutide, therefore increasing the likelihood of semaglutide being a cost-effective treatment (see Final Appraisal Document [FAD] section 3.20). It agreed that the population with a BMI between 27 kg/m2 and 30 kg/m2 were not generally at high enough risk for semaglutide use (see FAD section 3.4). The committee noted that maintaining weight loss following bariatric surgery is challenging (see FAD section 3.1) and that semaglutide could be useful for treating weight regain after bariatric surgery (see FAD section 3.2). However, no evidence was presented for maintaining weight in people who had had previous bariatric

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				surgery, so this population was not considered further by the committee.
27	NHSE expert	Gary McVeigh	NHSE recognises advice to committee that the appropriate setting for follow-up of obese patients, suitable for Semaglutide, would be within a specialist weight management (Tier 3) service. NHSE also recognise advice to the committee has been that patients can remain in Tier 3 services for a maximum of 2 years when responders to Semaglutide will then be required to stop the drug and will be discharged from the service with no further access to treatment. NHSE has expressed the view that it is inappropriate to use QRISK-3 to predict 10-year risk for adverse cardiovascular outcomes for a time-limited use of Semaglutide when regain in weight and loss of benefit on weight associated surrogate cardiovascular risk factors is inevitable. NHSE notes the recent publication of real-world data from a UK population that was not available to committee at the time of approval of Liraglutide. These data provide objective real-world quantification of the effects of intentional weight loss on obesity related CVD risk factors (Type 2 diabetes mellitus, hypertension and dyslipidaemia) and CV outcomes (atrial fibrillation, heart failure, unstable angina and myocardial infarction). Using data from CPRD-GOLD database cohorts were defined as having stable weight (-5% to +5%) or weight loss (- 25% to -10%). The stable weight cohort comprised 523,138 individuals and the weight loss cohort 48,823 individuals. The median age at the beginning of the follow-up period was 55 years and the follow-up time was median 6.3 years. The median weight loss was 13% compared with controls and the lower BMI , maintained over time, was associated with significant reductions in T2DM, blood pressure and improvements in dyslipidaemia. The beneficial impact on surrogate risk factors for CV disease were	Thank you for your comment. The committee recognised that the use of risk equations was associated with uncertainty and that the risk equations used in the model were not designed for estimating long-term risk when using an intervention with a time limited benefit (see Final Appraisal Document section 3.16). The committee recognised the real-world evidence that did not show a reduction in cardiovascular events related to sustained weight loss alone. However, the committee accepted that there was no data available on the effect of semaglutide on long-term cardiovascular outcomes, and it agreed that even a temporary improvement in weight, diabetic status and other risk parameters seen with semaglutide in STEP 1 would likely have some benefit. The committee noted a scenario analysis conducted by the ERG which showed that excluding cardiovascular benefits from the model had a small impact on the cost effectiveness estimate. Despite the uncertainties associated with the use of risk equations, the committee concluded that it had not been presented with an alternative method for estimating long-term health outcomes and that they were the only method available.

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			not associated with any benefit in any of the CV outcomes of atrial fibrillation, heart failure, unstable angina or myocardial infarction. NHSE note the very large sample size and the prolonged duration of follow-up of the weight loss and stable weight cohorts. Importantly, NHSE note the baseline 10-year risk for future myocardial infarction/stroke, based on QRISK-3, in the real-world cohort is approximately x3 that for the population included in the STEP-1 trial, due largely because of the older age at the beginning of follow-up and a greater percentage of male participants. Despite being at greater risk for adverse CV outcomes, no such signal was evident in the real-world weight loss participants compared with the control participants. NHSE is not aware of any CV outcome trial planned for a population similar to that in the STEP-1 trial and suspects such a trial will never be undertaken due to logistical and other challenges involved in setting up such a trial.	
28	NHSE expert	Gary McVeigh	All patients responding to Semaglutide will be required to stop the drug and will be discharged from the specialist weight management service with no further access to the drug.	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be

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				accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
29	NHSE expert	Gary McVeigh	The analysis implies it is appropriate to use QRISK-3 to predict the 10-year risk for MI/CVA using a time-limited (maximum -2 years) administration of Semaglutide when weight regain is inevitable and there is loss of effect on the surrogate CV risk factors. QRISK-3 should not be used in this way and the NHSE view is that this analysis is inappropriate. In addition, NHSE notes the potential for adverse mental and physical outcomes for responders to the medicine who simultaneously lose access to Semaglutide and access to SWMS at 2 years.	Thank you for your comment. The committee recognised that the use of risk equations was associated with uncertainty and that the risk equations were not designed for estimating long-term risk when using an intervention with a time limited benefit (see Final Appraisal Document section 3.16). It agreed that even a temporary improvement in weight, diabetic status and other risk parameters seen with semaglutide in STEP 1 would have some benefit, although this was difficult to quantify. The committee was aware that stopping treatment, which is associated with weight regain on average, may have a detrimental psychological impact (see FAD section 3.12). However, it agreed that specialist weight management services are the only appropriate setting for semaglutide treatment, and that these services are limited to 2 years access on average.
30	NHSE expert	Gary McVeigh	Given the real-world evidence, indicating no CV outcome benefit in a higher risk population for adverse CV outcomes compared with the participants in the STEP-1 trial, NHSE believes there is no evidence to support any CV outcome benefit for a time-limited use of the drug. Even if the drug were to be continued and	The committee recognised the real-world evidence that did not show a reduction in cardiovascular events related to sustained weight loss alone. However, the committee accepted that there was no data available

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			patients continue to respond, current evidence suggests that no benefit on CV outcomes can be assumed, at least up to 7 years with maintenance of weight loss. Assuming no CV benefit markedly increases the ICER with time-limited (maximum-2 years) use of the drug.	on the effect of semaglutide on long-term cardiovascular outcomes, and it agreed that even a temporary improvement in weight, diabetic status and other risk parameters seen with semaglutide in STEP 1 would likely have some benefit. The committee noted a scenario analysis conducted by the ERG which showed that excluding cardiovascular benefits from the model had a small impact on the cost effectiveness estimate (see Final Appraisal Document section 3.16).
31	Other	Prevention Team, NHSE England and NHS Improvement	The response below is an addendum to the submission by NHSE&I clinical advisor Gary McVeigh and the NHSE&I commercial directorate. NHS England and NHS Improvement (NHSE&I) has sought advice from the Obesity Tier 3 & 4 expert advisory group, chaired by Dr Jonathan Valabhji (National Clinical Director for Obesity and Diabetes) and agrees with the advice to the committee that the appropriate setting for follow-up of obese patients, suitable for semaglutide, would be within a specialist weight management (Tier 3) service. This ensures that semaglutide can be used within its license as an adjunct to a reduced-calorie diet and increased physical activity for weight management and ensures clear clinical governance arrangements are in place. NHSE&I disagrees with the proposed recommendation for semaglutide to be prescribed for a maximum duration of 2 years. The proposed time-limited access to treatment creates an artificial stopping point, not based on clinical evidence; once reached and treatment is stopped, there is evidence that patients will regain weight, as a result reducing the cost benefits of prescribing semaglutide. This will likely lead to some patients requesting re-referral into specialist weight management	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed (although this may be shorter in different areas of the country) and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12).

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			services, reducing cost-effectiveness further. NHSE&I does not nationally recommend a maximum duration that patients can access NHS obesity services. Applying a two-year limit to the prescribing of semaglutide could result in pressures on other services within the obesity pathway. We are aware that the committee has been informed that access to Tier 3 specialist weight management services is limited to 2 years; however, this does not reflect any national NHS guidance on the commissioning of specialist weight management services that we are aware of. The removal of the 2 year stopping rule would require remodelling for the delivery of the intervention. We insist that any significant change to the recommended eligibility criteria, such as alteration in the co-morbidities (e.g. making pre-diabetes a pre-requisite), undergoes a further round of public consultation. NHSE&I would like to reiterate the need to have full sight and approve any significant proposed changes to the TA recommendations for semaglutide.	Therefore, the committee recommended that semaglutide is given for a maximum for 2 years. The committee agreed that assumptions around weight regain are uncertain, however it heard from clinical experts that on average it would be expected that weight lost with semaglutide would be regained after around 2 to 3 years after stopping treatment (see FAD section 3.13). Weight regain within 3 years was included in the company's model and the committee noted a scenario analysis which showed that there was a modest impact on the cost effectiveness results when an assumption of weight regain over 2 years was included in the model instead.
32	Other	Prevention Team, NHSE England and NHS Improvement	The product license does not restrict treatment to 2 years for prescription of semalgutide. There is no national NHS direction on duration that patients have access to specialist weight management services; limiting the access to semaglutide to 2-years should be reassessed.	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section

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				3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed (although this may be shorter in different areas of the country) and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
33	Other	Prevention Team, NHSE England and NHS Improvement	Following engagement with the NHSE&I Tier 3 & 4 Obesity Expert Advisory Group, the removal of the 2 year maximum time period for prescription of semaglutide was unanimously agreed. A 2 year time limited window for prescription creates an artificial deadline for patients to stop the treatment; [redacted] This will impact costs over time, leading to an increase – we ask that this is considered to reflect the cost effectiveness in the real world. We believe that if a treatment duration was longer than 2 years that the cost-effective value would be higher.	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12).

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				Therefore, the committee recommended that semaglutide is given for a maximum for 2 years.
34	Other	Prevention Team, NHSE England and NHS Improvement	As a result of the removal of the 2 year stopping rule and a remodelling of the intervention, any significant further alterations to the recommended eligibility criteria of semaglutide should undergo an additional round of public consultation.	Thank you for your comment. The 2-year stopping rule has not been removed from the recommendation. No further significant alterations have been made to the recommendations from the recommendations in the Appraisal Consultation Document, therefore, no further public consultation was performed.
35	Other	Prevention Team, NHSE England and NHS Improvement	The current eligibility recommendations for semaglutide with a 2 year stopping rule would leave us out of line with the license and the rest of Europe.	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended

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				that semaglutide is given for a maximum for 2 years.
36	Company	Novo Nordisk	Novo Nordisk welcomes NICE's preliminary decision to recommend semaglutide 2.4mg for treatment in specialist weight management services (SWMS) recognising that the treatment is clinically and cost effective in a population with a high unmet need. We are grateful for the opportunity to provide our comments, which aim to improve the clarity of some aspects of the Appraisal Consultation Document.	Thank you for your comment.
37	Company	Novo Nordisk	The word 'exceptionally' in Section 1.1 is imprecise and may infer that only some people with BMI 30-34.9 in SWMS are eligible for treatment. In Section 3.2 it is highlighted correctly that people with a BMI of 30 kg/m2 to 34.9 kg/m2 are already eligible for those services. Rapid research conducted with commissioners, chief pharmacists and other local payers indicated that the use of the word 'exceptionally' could result in clinicians having to provide supporting evidence of why a patient is considered exceptional which may require approval on a case by case basis via an exceptional case panel. To maintain consistency and clarity in the recommendation and to avoid adding to the administration burden, the word 'exceptionally' should be removed.	Thank you for your comment. The term exceptionally has been removed from the recommendation.
38	Company	Novo Nordisk	The reference to 'tier 3' in Section 1.1 is inconsistent with the description of SWMS in Section 1.2. We suggest using the term 'specialist weight management services' in Section 1.1 to improve consistency while still reflecting the committee discussion. We suggest the following wording in Section 1.1 and across the document: *'a BMI of 30.0 kg/m2 to 34.9 kg/m2 for whom conventional treatment has been unsuccessful and who are suitable for referral to specialist weight management services according to NICE guidance on obesity*[1,2]'. 1. National Institute for Health and Care Excellence. Obesity: identification, assessment and management [CG189]. 2014. (Updated: 27 November 2014) Available	Thank you for your comment. Recommendation 1.1 has been amended to refer to specialist weight management services, rather than tier 3 services. This wording has also been amended throughout the Final Appraisal Document where appropriate.

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			at: https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925. Accessed: 25 February 2022. National Institute for Health and Care Excellence. Obesity: clinical assessment and management (QS127). 2016. (Updated: May 2020) Available at: https://www.nice.org.uk/guidance/qs127/resources/obesity-clinical-assessment-and-management-pdf-75545363615173. Accessed: 25 February 2022.	
39	Company	Novo Nordisk	We welcome the recommendation for treatment in SWMS with multidisciplinary input. To note, we heard at committee that a wide variety in service provision exists across the UK with some SWMS not being described formally as a tier 3 or tier 4 service, and with some provided in community care and others in a secondary care setting. To account for the variability of SWMS across the UK and not to further exacerbate any potential inequalities in service provision, we suggest changing the wording in Section 1.2 to 'such as *but not limited to* tier 3 or tier 4 services'.	Thank you for your comment. Recommendation 1.1 has been amended to refer to specialist weight management services providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4).
40	Company	Novo Nordisk	In Section 1, page 4 it is stated that 'It is appropriate to use semaglutide alongside intensive lifestyle interventions that are provided in specialist weight management services because this is in keeping with the clinical trial'. We would suggest removing the word 'intensive' because it is inconsistent with the license and the definition of lifestyle intervention in the STEP trials considered relevant for this appraisal (STEP 1, 2, 5, 8). Semaglutide is licensed to be used as an adjunct to a reduced-calorie diet and increased physical activity. The term 'intensive lifestyle interventions' is usually associated with intensive behavioural therapy as seen in the STEP 3 trial which, as the ERG and committee agreed, is not reflective of clinical practice in England.	Thank you for your comment. The word intensive has been removed from section 1 of the Final Appraisal Document.
41	Company	Novo Nordisk	In the title of Section 3.19 it is stated that 'The ICERs for	Thank you for your comment. The

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			semaglutide compared with diet and exercise are uncertain, so a restricted version of the company's original target population is appropriate'. We would like to clarify that the company's original target population as noted on page 9 of the company submission is for people with a BMI of ≥ 30 mg/kg2 in the presence of at least one weight-related comorbidity for patients who are eligible for treatment within specialist weight management services. It is therefore unclear how the recommended population differs.	company's original target population as specified in the company submission to NICE was for "adults with a BMI of ≥30kg/m2 in the presence of at least one weight related comorbidity". The company submission states that these people are eligible for treatment within specialist weight management services. However, the committee noted that NICE's clinical guideline on obesity: identification, assessment and management recommends considering referral to tier 3 services in specific circumstances. For people with a BMI of 30kg/m2 to 34.9kg/m2 with at least 1 weight related comorbidity, semaglutide is only recommended for people who meet the criteria for referral to specialist weight management in NICE's clinical guideline on obesity and not the company's full target population.
42	Company	Novo Nordisk	In Section 3.3, page 8 the following is mentioned 'They also stated the importance of only offering semaglutide with these interventions because this was a requirement in the trial that showed favourable results. The clinical experts did not consider that semaglutide is a 'stand-alone' treatment.' We would like to clarify that the use of semaglutide 2.4mg as an adjunct to a reduced-calorie diet and increased physical activity is indicated by the treatment's MHRA license and is the main reason the treatment should not be used as a 'stand-alone'.	Thank you for your comment. Section 3.3 of the Final Appraisal Document includes information about the specification of using semaglutide as an adjunct to diet and exercise within the marketing authorisation, in addition to the clinical expert statements. No changes related to this comment were made.
43	Company	Novo Nordisk	In Section 3.6, it is stated that 'The population in STEP 1 does not reflect the population distribution of overweight and obesity in clinical practice' and that the committee concluded 'the population in STEP 1 had a larger proportion of a high-risk population and did not reflect the population distribution of overweight and obesity in clinical practice'. We would like to	Thank you for your comment. Section 3.6 of the Final Appraisal Document has been updated to specify that the STEP 1 population does not reflect the population distribution of overweight and obesity in the general population. This section describes

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			request clarification on whether this sentence refers to the overall population seen in general clinical practice or the specialist weight management services population. Our understanding is that the statement applies to a general clinical practice and not SWMS where the treatment is positioned. We would propose the latter sentence to be followed by this text *'However the treatment is expected to be prescribed in specialist weight management services where the proportion of high-risk population is larger than in general clinical practice and more aligned with the population in STEP 1'*.	the misalignment between the STEP 1 trial and the potential population who could be eligible for specialist weight management services, therefore no further changes have been made to this section.
44	Company	Novo Nordisk	In Section 3.7 it is stated that 'The clinical experts explained that if someone with type 2 diabetes needs specialist weight management then it would be appropriate for them to have treatment for obesity within a tier 3 service (or equivalent).' To avoid any confusion, we would propose changing the wording of this sentence to 'The clinical experts explained that if someone *with obesity* and type 2 diabetes needs specialist weight management then it would be appropriate for them to have treatment for obesity within a tier 3 service (or equivalent).' Moreover, this section should acknowledge that the company provided cost effectiveness estimates for this population using data from STEP 2.	Thank you for your comment. Section 3.7 of the Final Appraisal Document (FAD) has been updated to clarify the population being discussed in this section is people with obesity and type 2 diabetes. Section 3.7 describes the clinical evidence available for people with obesity and type 2 diabetes. Section 3.20 describes the scenario analysis provided by the company including people with type 2 diabetes in the model, and it is not necessary to also include this within the clinical evidence section of the FAD.
45	Company	Novo Nordisk	In the title of Section 3.10 it is noted that 'The company's model is only suitable for decision making for treatment in specialist weight management services'. This sentence is misleading as it is the data used in the model that makes the model suitable for decision making for treatment in specialist weight management services. The company submission is targeted to a population with a BMI of 30 or more plus 1 or more weight related comorbidity who are referred into a SWMS, consistent with the available data from the STEP programme.	Thank you for your comment. Section 3.10 in the Final Appraisal Document has been updated to reflect that the model is appropriate for decision making, and that the assumptions included in the model are appropriate for use within a specialist weight management service.
46	Company	Novo Nordisk	In Section 1.1, we would suggest the text referring to different BMI criteria for specific ethnicities to be moved to a separate bullet point. This amendment should prevent any confusion on	Thank you for your comment. The recommendations are in line with NICE editorial styles. No changes to the

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			the BMI thresholds.	recommendation on BMI thresholds was made.
47	Company	Novo Nordisk	In the title of Section 3.14 it is noted that 'The assumption that all people develop type 2 diabetes after a cardiovascular event is not correct'. This assumption refers only to people with non-diabetic hyperglycaemia. Additionally, this sentence is misleading because an assumption is required due to the unavailability of data. We point out that the alternative approach, i.e., assume that risk after a cardiovascular event is equivalent to patients with normal glucose control is also not correct, with the truth lying somewhere on this continuum. For accuracy, we would suggest replacing this sentence with *'The model assumes that all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event'*. Additionally, in page 20 we would suggest replacing the word 'hyperglycaemia' with 'non-diabetic hyperglycaemia'.	Thank you for your comment. Section 3.15 in the Final Appraisal Document has been amended to reflect these comments.
48	Company	Novo Nordisk	Semaglutide is indicated for type 2 diabetes in different dosages. To avoid confusion, we would recommend replacing 'semaglutide' with 'semaglutide *2.4mg*' across the document.	Thank you for your comment. Section 2.2 describes the dosage of semaglutide for managing overweight and obesity according to the marketing authorisation. The Final Appraisal Document Section 3.7 also states that a lower dose of semaglutide is available for managing type 2 diabetes. It is not necessary to include further detail on the dosage of semaglutide within the FAD.
49	Company	Novo Nordisk	In Section 3.5 it is stated that 'the appropriate comparators for semaglutide were… liraglutide for people with a BMI of 35 kg/m2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease.' We suggest changing this to 'liraglutide 3mg *as an adjunct to lifestyle intervention*' to be consistent with the license for liraglutide 3mg (Saxenda®).	Thank you for your comment. The Final Appraisal Document section 3.5 has been amended to refer to liraglutide plus weight management support, diet and exercise as the appropriate comparator for people with a BMI of 35 kg/m^2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease.
50	Company	Novo Nordisk	In Section 3.9 it is stated that 'liraglutide is the appropriate	Thank you for your comment. The Final

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			comparator for people with a BMI of 35kg/m2.'. We suggest changing this to '*liraglutide 3mg as an adjunct to lifestyle intervention'* to be consistent with the license for liraglutide 3mg (Saxenda®).	Appraisal Document section 3.9 has been amended to refer to liraglutide plus weight management support, diet and exercise as the appropriate comparator for people with a BMI of 35 kg/m^2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease.
51	Company	Novo Nordisk	In Section 3.17 it is stated that 'the ERG base case included some of the same assumptions as the company's with the following differences: the annual cost of sleep apnoea is £1,081 (compared with the company's assumption of £274)'. We would like to clarify that the company's assumption is £1,081 and the ERG assumption is £274.	Thank you for your comment. This correction has been made in section 3.18 of the Final Appraisal Document.
52	Company	Novo Nordisk	In Section 3.19, the average BMI in STEP 1 is described incorrectly and inconsistently. The average BMI in STEP 1 was 39.7. Please update the document with the correct figure.	Thank you for your comment. The average BMI of STEP 1 has been reported as 39.7kg/m2 in section 3.20 of the Final Appraisal Document. It is noted that the average BMI in the economic model for the relevant subgroup was 38.7 kg/m2.
53	Professional group	Royal College of Physicians	We strongly disagree with the recommendation that semaglutide 2.4 mg be stopped after 2 years. Obesity is recognised as a chronic relapsing progressing medical condition/disease like type 2 diabetes. Obesity is associated with multiple co-morbidities and reduced quality of life. Weight loss leads to improvement and/or remission of obesity-related comorbidities and improved quality of life. Importantly, the degree of improvement in health and quality of life depends upon the amount of weight loss, with greater improvements seen with greater weight loss. The improved efficacy of semaglutide 2.4 mg compared to currently available weight loss medications means that the health benefits and improvements in quality of life are greater. However, we know that when people stop taking any weight loss	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight

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			medication, they regain the weight lost, in keeping with obesity being a chronic medical condition. The findings from the STEP 4 trial show that participants regained the weight lost when they stopped semaglutide. This means that most people who will receive semaglutide for 2 years will then regain the weight lost and experience a worsening/relapse of their obesity-related comorbidities. This is also likely to have a negative impact upon their psychological well-being. We recommend that treatment is continued in patients who achieve weight loss and improvement in their health. However, if patients have to stop treatment at 2 years, then there needs to be clear guidance regarding restarting treatment e.g., regain of >5% body weight or recurrence of obesity-related complications.	management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, despite acknowledging evidence from the STEP 4 trial that weight is regained after semaglutide is stopped (see FAD section 3.13), the committee recommended that semaglutide is given for a maximum for 2 years. The committee acknowledged that retreatment might be appropriate for some people if they were eligible for treatment again according to the same starting criteria (see FAD section 3.14). Section 3.14 has been added to the FAD for clarification around retreatment.
54	Professional group	Royal College of Physicians	Our experts question whether the committee considered the appropriateness of using semaglutide 2.4 mg in patient groups with a BMI between 30 and 34.9 who are required to lose weight prior to another surgical procedure in order to make this safer e.g., prior to surgery for endometrial cancer or other gynae procedures? It would also be helpful to know whether women who need to reach a BMI of ≤30 prior to being eligible for IVF would be included. People with serious mental illness are at specific increased risk of metabolic consequences of obesity and have more complications after bariatric surgery which is the only alternative currently available. Although there is evidence for liraglutide in counteracting the harmful effects of anti-psychotic medication we are not aware of any evidence for semaglutide specific to this population. Please can future recommendations consider this	Thank you for your comment. The committee recommended semaglutide for a group of people most at risk of the adverse event associated with obesity. For people with at least 1 weight related comorbidity and a BMI between 30kg/m2 and 34.9kg/m2, semaglutide is recommended for people in specific circumstances based on criteria in NICE's clinical guideline on obesity: identification, assessment and management. These criteria include when surgery is being considered. When this guidance is reviewed, the appraisal committee will take into account any relevant evidence that suggests a clinically justified reason to consider

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			group separately – there is a trial ongoing the results of which should inform: Clozapine Obesity and Semaglutide Treatment (COaST). - qcmhr	specific subgroups separately, such as people with severe mental illness.
55	Professional group	Royal College of Physicians	The current NICE guideline regarding obesity management (2014) states that people with a BMI ≥35 with recent onset type 2 diabetes (T2DM) should have an expedited referral for assessment for bariatric surgery. This is based on the strong evidence that the likelihood of remission of type 2 diabetes after bariatric surgery is greatest when surgery is undertaken earlier. Currently, few patients who should be offered bariatric surgery have this discussed with them. We are concerned that people with new onset T2DM and a BMI of ≥ 35 will be offered semaglutide 2.4 mg and not referred for assessment for bariatric surgery as per current NICE guidelines. At the moment there are no data regarding the long-term impact of semaglutide upon remission of T2DM. We suggest that this recommendation regarding referral for assessment for bariatric surgery is reiterated in this recommendation along with the fact that the long-term impact of semaglutide 2.4 mg upon T2DM remission is not known or that this is considered by the current guideline development group that is updating the obesity prevention and management guidelines.	Thank you for your comment. The implementation of the recommendations in NICE's guideline on obesity: identification, assessment and management, is outside the remit for this appraisal. Your comment has been passed onto the guideline updates team and will be considered within the review of the obesity guideline suite which is currently ongoing.
56	Professional group	Royal College of Physicians	We are concerned that the patchy provision of tier 3/tier 4 services will mean that there will be a postcode lottery with regards to accessing semaglutide 2.4 mg in the absence of additional funding for the establishment of new services. Currently, access to NICE TA approved liraglutide 3mg for weight management is limited via the proviso that this can only be prescribed by tier 3 services.	Thank you for your comment. The committee recognised that specialist weight management services are not available everywhere across the country and that this results in a postcode lottery for access to services. However, it considered that specialist weight management services are

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			Specialist weight management services already have a significant back log of patients waiting to be seen due to COVID-19. Without additional workforce expansion the implementation of this NICE TA will be difficult. At the moment there is little integration between Tier 2 and Tier 3 services. We suggest a shared-care model between specialist Tier 3 / Tier 4 services and Tier 2 /primary care weight management services. However, we appreciate that service structure is not the remit of NICE.	the only appropriate setting for semaglutide treatment (see Final Appraisal Document section 3.23). Implementation and the service structure for NHS weight management is not within the remit of this appraisal, but the committee welcomed any review of NHS services for overweight and obesity (see section 3.23).
57	Web commentator	ASO	Are the recommendations sound and a suitable basis for guidance to the NHS? Overall the ASO welcomes the NICE appraisal and feel that it will benefit many patients with obesity in view of the wide eligibility criteria. The concerns raised by the ASO Trustees are summarised below: 1. It is unusual for a chronic disease to be treated for 2 years only. Medications for other chronic conditions, some of them expensive, are continued for life (e.g. dyslipidaemia with PCSK9 inhibitors or inflammatory conditions with biological therapies). The two year cutoff may make cost effectiveness sense but not clinical sense. Guidance on what the options for patients are after the 2 year course would be very useful. 2. "exceptionally, a BMI of 30.0 kg/m2 to 34.9 kg/m2": This eligibility criterion is vague. What does exceptionally actually mean in practice? 3. In practice, it is not clear how this should be funded. a. If the medication is started in a hospital tier 3 setting, would it	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). Therefore, the committee recommended

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			be possible for the prescriptions to be continued by primary care (a model similar to diabetes care) or would prescriptions and therefore associated costs remain in secondary care? b. It would be useful if the appraisal could clarify whether the medication can be prescribed in a community tier 3 setting. 4. Concerns were raised regarding the implementation of the guidance with the available resources in tier 3/4 settings. The lack of staff needed to initiate the medication and conduct the follow-up will mean that long waiting lists will be formed very rapidly. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Only 40-50% of the country has tier 3 service provision, thus this guidance will disadvantage the other half of the population that do not have these services available to them. This raises the question as to whether the medication should be routinely prescribed by primary care as part of a tier 2 service.	that semaglutide is given for a maximum for 2 years. It is outside the remit of this appraisal to provide guidance on care for people after treatment is stopped. The term exceptionally has been removed from the recommendation. The recommendations state that semaglutide should only be used within a specialist weight management service. These services can be found in primary and secondary care and prescription should be made within the service the person is referred to by the specialist within that service. Prescription outside a specialised weight management service is not recommended. Implementation of the recommendations is outside the remit of this appraisal. However, the committee welcomed any review of NHS services for overweight and obesity (see section 3.23). The committee noted that specialist weight management services are not available throughout the country (see FAD section 3.2). However, the committee concluded that specialist weight management services are the only appropriate setting for semaglutide treatment. It agreed that the current tiered system for obesity

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				management is not ideal and suggested that this system should be reconsidered (see FAD section 3.23).
58	Web commentator		Comments on the ACD: Any stopping criteria should be driven my medical need (e.g. evidence of toxicity with repeated dosing) or best-available evidence (e.g. the drug stops working). In the case of semaglutide, we have high-quality evidence that it is neither toxic nor ineffective long-term. It is clinically appropriate therefore to continue long-term at least in a proportion of the population who are not eligible for surgery or cannot sustain weight loss with lifestyle modification. NICE must review the cost-effectiveness of continued treatment as this will happen in clinical practice. As we anticipate major implementation challenges with the stopping rule requirement of this TA, a proportion of patients will continue treatment long-term (as they continue to benefit). Under the assumption that the decision rule introduced by the manufacturer exists only because without it, the drug is not cost-effective, NICE must acknowledge that they are committing the NHS to prescribe a drug which is not cost-effective by stealth. Semaglutide is a chronic condition. Whilst a proportion of patients be able to discontinue treatment (after successful lifestyle modification, or surgery) a not insignificant proportion of patients will require lifelong treatment. The requirement for life long treatment is is acknowledged by the patient experts and the Committee in Section 3.12. A stopping rule for all patients is not clinically appropriate therefore will have major implementation challenges for the NHS. Novo Nordisk has a track record of introducing clinically	Thank you for your comment. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion (Final Appraisal Document [FAD] section 3.3). It agreed that for a long-term condition like obesity, it was not ideal that specialist weight management services were only available for 2 years (see FAD section 3.12). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). The committee agreed that it could only make recommendations based on the current understanding of the structure of specialist weight management services, which it heard were not accessed for longer than 2 years. Therefore, the committee recommended that semaglutide is given for a maximum for 2 years. The implementation of the guidance is

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			unjustifiably stopping rules that are not adhered to in clinical practice. Liraglutide 1.2mg was given a positive TA for type 2 diabetes as NICE found the drug to be cost-effective if a major improvement in both HbA1c AND weight were seen at 6 months. In clinical practice however a significant proportion patients experienced either one or the other of these benefits. The TA required that liraglutide is discontinued for these patients are (as both benefits were not observed) however in practice this rarely happened as patients could see improvement in their clinical condition. Predictable and significant non-compliance to this stopping rule effectively meant that NICE introduced a drug in NHS practice which was not cost-effective. NICE must reconsider their approach to stopping rules. We know it is clinically appropriate for patient to continue semaglutide drug long-term, therefore NICE must assess the cost-effectiveness of this approach. We acknowledge that the same decision rule as exists for liraglutide 3 mg however it is not acceptable for NICE to continue with this error of judgement. This stopping rule should be removed and the cost-effectiveness of life-long semaglutide considered. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. NICE is endorsing a 2 year treatment course for a chronic condition; this approach is not evidence based and has major implementation challenges. The 2 year decision rule is a feature of the economic analysis introduced by the manufacturer to make the drug look more cost-effective than it is. NICE should review the cost-effectiveness of long-term treatment. Are the recommendations sound and a suitable basis for guidance to the NHS?	outside the remit of this appraisal.

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			No. NICE is endorsing a 2 year treatment course for a chronic condition; this has major implementation challenges. Insufficient advice is provided for the significant proportion of patients who will regain weight after the 2 year treatment window. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No	
59	Web commentator		We welcome the addition of Semaglutide as a proven effective treatment choice for people living with obesity and overweight. The current pharmacological treatment options are limited to Orlistat - which is poorly tolerated in many people and rarely used - and Liraglutide for those with a BMI over 35kg/m2 so the addition of Semaglutide offers greater choice to more people living with this condition who want to lose weight. Although the submitted trial data did not include people with type 2 diabetes, the summaries highlight the benefits of this treatment for this group. We feel this is much-needed given what we know about the effectiveness of the treatment and increasing prevalence of type 2 diabetes in the population. Our statistics show that the prevalence of diabetes has more than doubled in the last 15 years with 4.9 million now living with the condition in the UK and 90% of these having type 2 diabetes. A further 13.6 million people are at an increased risk of developing type 2 diabetes. Obesity is the most significant modifiable risk factor and accounts for as much as 85% of the overall risk of developing type 2 diabetes; it is also associated with difficulties managing blood glucose levels and an increased risk of complications in those already diagnosed. Semaglutide is	Thank you for your comment.

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			therefore an important step in mitigating this and supporting people with or at risk of type 2 diabetes to lose weight improve their underlying health. Furthermore, Semaglutide is administered as a once-weekly injection compared to Liraglutide which is a once-daily injection so it is appealing to many people who prefer less injections for various reasons such as needle phobia.	
60	Web commentator		Has all of the relevant evidence been taken into account? With regard to the expected weight re-gain after discontinuation of semaglutide: The findings of the paper: Le Roux et al. Lancet 2017 (showing the 3 year outcomes of the SCALE obesity pre-diabetes trial) demonstrated significant rapid weight regain in the first 12 weeks after stopping liraglutide. The drug was stopped at week 160 in this trial, weight gain at week 172 is reported. Extrapolating from the published data and graphs in that paper it is reasonable to assume that all the weight advantage of liraglutide would be lost within 6-12 months of discontinuation. It is reasonable to assume that semaglutide discontinuation would follow a similar clinical course and that all of the weight advantage would be lost over period of 6-12 months. This evidence does not appear to have been considered in section 3.13. It should be taken into account. Reference: Le Roux et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017 Apr 8;389(10077):1399-1409. Patients who have had previous bariatric surgery and weight regain should be excluded from these recommendations because they represent an entirely different cohort of patient as	Thank you for your comment. The committee considered the evidence from the SCALE Obesity and Prediabetes trial. It heard from the ERG that extrapolating from evidence at 12 weeks to longer periods may not be appropriate as it is unknown if weight regain will be linear. The committee also heard from clinical experts that the SCALE trial may not be that helpful for estimating weight regain due the 12 week follow up and lower overall weight loss than expected with semaglutide in practice. They suggested on average, they would expect weight to be regained after stopping semaglutide over 2 to 3 years. The committee also noted that weight loss with semaglutide is likely to be greater than with liraglutide and therefore weight regain is likely to be faster after liraglutide treatment (see Final Appraisal Document section 3.13). The committee was not aware of any evidence to be able to consider people who have had previous bariatric surgery as a subgroup, and therefore was not able to make specific recommendations for this population.

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			compared to surgically naive patients. The assumptions of the cost-effectiveness analysis do not apply to the post-surgical group. Patients who have already had bariatric surgery are at a different phase of their obesity journey. The majority will have had prolonged severe morbid obesity in the past and may have already developed complications related to obesity. The Markov state-transition cohort model being used describes 11 health states, but the patients who have previously had morbid obesity, bariatric surgery weight loss and then weight-regain are not comparable to the health states used in the model. Their metabolic risk profile, complication risk and service use is not comparable to the group that are using semaglutide as a relatively early intervention for obesity.	
61	Web commentator		Are the recommendations sound and a suitable basis for guidance to the NHS? It should include patients experiencing a weight gain due to taking SSRI/Anti psychotic medication. Particularly as this weight gain is largely unavoidable and can contribute to levels of non concordance with medication for this reason Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? As above	Thank you for your comment. The recommendations do not exclude people who experience weight gain due to taking selective serotonin reuptake inhibitors (SSRIs) or antipsychotic medication. The committee was aware that access to specialist weight management services is restricted for some people with severe mental illness (see Final Appraisal Document section 3.23). However, it considered that these services are the only appropriate setting for semaglutide treatment. The committee was not aware of any evidence to be able to consider people taking SSRIs or antipsychotic medication as a separate subgroup and therefore was not able to make specific recommendations for this population.
62	Web commentator		We are writing to raise concerns that the consultation document as it stands unlawfully discriminates against people with severe	Thank you for your comment. The committee considered these comments that

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			mental illness (SMI). SMI is defined as “psychological problems that are often so debilitating that patients’ ability to engage in functional and occupational activities is severely impaired”. Schizophrenia and bipolar disorder are examples of SMI. People with SMI experience substantial health inequalities and have poorer physical health than those without SMI(1). Notably, rates of obesity are 80% higher in people with SMI. People with SMI are considered to have a disability under the Equality Act 2010. Therefore, this guidance needs to consider their particular needs. In its current form, this guidance will substantially limit the access of people with SMI to treatment with semaglutide by reason of their disability, by both direct and indirect discrimination. As such, we believe it may unlawfully discriminate against this group. The main barrier to access to this treatment for people with SMI is the requirement that semaglutide be provided only within a Tier 3 obesity service. People with SMI are discriminated against by Tier 3 services both directly and indirectly. There is evidence of direct discrimination against people with severe mental illness by Tier 3 obesity services. For example, a simple Google search of ‘tier 3 obesity services’ shows evidence of explicit exclusion of this group in all three of the first three returned referral criteria: - “Patients who have active mental health problems, i.e. are under the care of the community mental health teams or in-patient care, should not be referred to the Obesity Management Programme”(2) - Exclusion criteria include “Clients with an unstable psychiatric disorder”(3) - Exclusion criteria include “Active psychosis”(4)	access to specialist weight management services is restricted for some people with severe mental illness (see Final Appraisal Document section 3.23). It discussed if semaglutide should be offered in different settings such as mental health services because of this. However, the committee considered that specialist weight management services are the only appropriate setting for semaglutide treatment as these can provide the necessary multidisciplinary specialist weight management interventions needed to provide semaglutide as a package of care, in line with its marketing authorisation. The evidence shows that semaglutide is effective when given alongside a programme of lifestyle interventions which are provided in specialist weight management services. The committee was not aware of any evidence that without these lifestyle interventions that semaglutide would be effective. It noted the comment that some secondary mental health services do provide advice and management of physical health. However, the committee agreed that this was not equivalent to the setting in the trial which included weight-loss orientated multidisciplinary treatment and there was no evidence that semaglutide would be effective in this setting. The committee agreed that specialist weight management services should be accessible to anyone who is

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			In addition to the direct discrimination by explicit exclusion of patients with SMI, there is also indirect discrimination. Most Tier 3 services demand a high level of active engagement by patients who are referred to them, and many require previous substantial self-directed efforts at weight loss before offering an intervention. People with SMI often have specific deficits such as avolition (lack of motivation to perform even rewarding or pleasurable activities) and lack of executive control (the ability to plan and carry out a complex series of actions). Both of these deficits mean that people with SMI would struggle to meet these criteria more than a person without SMI, due to their disability. This discrimination might be legal under the Equality Act, as Tier 3 services as they currently stand may lack the necessary skills to work effectively with this group. However, it is not clear where this group can access specialist weight management support – which may leave the NHS in breach of its duties under the Equality Act 2010. Some, but not all(5), secondary care mental health services do provide advice and management of physical health, including some lifestyle advice for weight management, to patients with severe mental illness. However, if this is felt to be equivalent to a Tier 3 service negating the need for specialist provision, then semaglutide would need to be available within this service. It is particularly unjust to limit access to a weight loss intervention for people with SMI. Much of the weight gain in SMI is iatrogenic. Most patients with SMI will be treated with a second-generation antipsychotic medication such as olanzapine, risperidone and clozapine. Patients with SMI are likely to take these medications for life. Weight gain is an almost universal side effect from these medications, as well as more widespread metabolic derangement which leaves people with SMI at elevated risk of most of the complications of obesity. Medication-related weight gain is a key driver of non-adherence with treatment for severe	eligible and able to engage with the interventions provided in these services, despite any comorbidities. The committee concluded that the current tiered system for obesity management is not ideal and suggested that this system, including referral criteria for people with severe mental illness should be reconsidered. However, this is not within the remit of the committee for this appraisal.

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			mental illness such as schizophrenia(6), and stopping or reducing medication often results in relapse of illness and the need for inpatient treatment – which can be devastating for the individual as well as costly to the NHS. Situating access to semaglutide within Tier 3 obesity services could be seen as a strategy for demand management. In people without SMI, this is justifiable; obesity for most people is a complex social and behavioural problem and effective strategies for behaviour change at the national level are preferable solutions to expensive pharmaceuticals. However, for people with SMI, obesity is much more likely to have a medical cause – as a medication side effect – rendering policy change less effective and pharmaceutical management more appropriate. Tier 3 services might also be inappropriate for people with SMI because there is strong evidence – from the STEPWISE trial – that even intensive diet and lifestyle programs have zero impact on weight in this group(7). Pharmacological management of weight gain therefore looks increasingly important for people with SMI. Liraglutide has been trialled in people with SMI, with positive results – around 6kg of weight loss with treatment(8,9), maintained at 1 year(10). This weight loss is clinically significant, and importantly was achieved without a concomitant intensive diet and exercise intervention. A major barrier to recruitment in one trial was the need to self-administer liraglutide as a daily injection – meaning semaglutide is a far more feasible treatment in this group. There are outstanding questions about the cost-effectiveness of semaglutide in people with SMI. However, there is reason to believe that prevention of co-morbidity associated with obesity may be more cost-effective in people with SMI. People with SMI are less able to self-manage diabetes effectively(11) and more likely to suffer complications(12,13). Both inpatient and	

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			outpatient costs are increased after MI for patients with SMI(14), and mental illness increases the likelihood of needing institutional care after stroke 6-fold(15). In conclusion, we believe that semaglutide should be offered to people with SMI via secondary care mental health services, and not within specialist weight management services. Failure to do so means direct discrimination against this group, entrenching the health inequalities which mean people with SMI die 10-20 years younger. Weight gain in people with SMI has been shown to be iatrogenic, not amenable to lifestyle change by the individual, and at least partly reversible by the daily use of liraglutide, which is similar to but less effective and convenient than semaglutide(16). We have a particularly great responsibility to offer individuals with SMI the same chance at the best possible treatment that is being given to the rest of the population.	
63	Web commentator		Comments on the ACD: Thank you. It is great that Semaglutide will be available to people with obesity on the NHS. However, I feel there is a need for more clarity around a few points: 1. What would you define as obesity-related comorbidity? 2. Will people post bariatric surgery be eligible for Semaglutide? Has a cost-benefit analysis been performed? 3. Including people with BMI 30-35 will lead to a big shift in the number of referrals from this cohort and the patient population in a tier-3 weight management service. This will have big implications on demand and service delivery; this needs to be taken into consideration. Saying ''exceptionally'' and then referring to NICE clinical guidelines on obesity, which say ''consider referral to tier-3 if: conventional treatment has been unsuccessful''. That means	Thank you for your comment. A wide range of weight-based comorbidities were included in the trial for people with a BMI over 30 kg/m2 and therefore reflected in the company's economic model. Therefore, the committee was not able to specify which weight-related comorbidities are included within the recommendation. The committee was not aware of any evidence to be able to consider people who have had previous bariatric surgery as a subgroup, and therefore was not able to make specific recommendations for this population. However, people who have had previous bariatric surgery are not excluded from the recommendations.

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			almost everyone will be eligible and it is not exceptional. Currently this cohort is not seen in a tier-3 service mainly because they are not asking for the referral. With the option of Semaglutide, more people will be asking to be referred to WMS. There is nothing wrong with that, but without the infrastructure to support this model, there will be lots of tension and disappointment for everyone involved. 4. More clarity in the recommendation around re-treatment with Semaglutide is needed. Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Yes Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes	The referral for specialist weight management services for people with BMI between 30 and 35 kg/m2 should continue to follow recommendations in NICE's clinical guideline on obesity: identification, assessment and management. It is outside the remit of this appraisal to make recommendations on implementation. Further information on retreatment with semaglutide has been included in section 3.14 of the FAD.
64	Web commentator		Comments on the ACD: Semaglutide will be welcome in the Tier 3 service and the BMI targets are appropriate and in line with the referral criteria to the Tier 3 service. There is a further need to specify assessment for	Thank you for your comment. The committee agreed that it is reasonable that people who have less than 5% weight loss after 6 months will stop treatment, in line with the marketing authorisation which

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			suitability/expectation management and monitoring of the effect of therapy for further prescription. Has all of the relevant evidence been taken into account? Existing evidence has been considered, however the lack of evidence in certain areas should equally be acknowledged. This concerns the use of GLP-1 in treating eating disorders with and without psychological therapies (and respective engagement in combination), clinical depression, GLP-1 use in bariatric workup and comparison with surgical outcomes. Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? There are reasonable within the limitations of research not representing real life complexities and with the lack of evidence regards long term use on weight loss. It would be beneficial for the clinicians to know when Semaglutide is no longer considered (cost)-effective and to be discontinued. Semaglutide will be welcome in the Tier 3 service and the BMI targets are appropriate and in line with the referral criteria to the Tier 3 service. These services may work in slightly different pathways, e.g. some may work more towards conservative management, whilst others work predominantly towards pre-surgical workup. Part of both is an evaluation of eating pathology and mental health needs which have a high prevalence in obesity populations, especially in those with higher BMIs. Externalising eating behaviour will be most amenable to target with drugs, whilst emotional eating and binge eating will require psychological support. Patients however may be referred and expect a ‘drug therapy fix’ and/or (plus additional surgical fix) and opt out of recommended psychological therapies. Evidence so far was unable to address these co-morbidities and research	specifies that this should be considered (Final Appraisal Document section 3.11). Further monitoring of treatment effect should be based on clinical judgement. It is not within the remit of this appraisal to consider evidence for use of GLP-1 inhibitors such as semaglutide for conditions other than overweight and obesity. The recommendations include a stopping rule that semaglutide treatment should be given for a maximum of 2 years. Semaglutide has been recommended as part of a package of care within specialist weight management services, which also provide multidisciplinary team support, such as psychological therapies. Referral for bariatric surgery should continue to follow recommendations in NICE’s clinical guideline on obesity: identification, assessment and management. The recommendations for semaglutide in this appraisal provide an additional treatment option which can be offered alongside other possible treatment options for which the person is eligible.

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			studies rarely recruit patients with mental health problems. I propose monitoring of the engagement with lifestyle change in addition to ongoing prescribing such as proposed with Saxenda. In addition, patients should choose whether to opt GLP-1 analogues or chose the surgical pathway as the two in parallel have 1) not been tested, alias no evidence, 2) it will not be possible to assess surgical readiness regards of underlying eating pathology such as restraint eating behaviours which underlie eating disorders. Latter may resurface after surgery and compromise long term success beyond 2 years after surgery. Thus, I would like to see GLP-1 treatments part of a separate referral/ Tier 3 treatment pathway to the bariatric surgical pathway with clear expectation management at the outset. In summary, it is unclear when to use GLP-1 analogues versus prepare patients to bariatric surgery and whether GLP-1 analogues should be continued if not showing any effect on weight loss. Inclusion of a discontinuation guideline within the 2 years of therapy is needed. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No concerns	
65	Web commentator		Are the recommendations sound and a suitable basis for guidance to the NHS? Rec 1.2 There is potential for confusion with the criteria for prescribing semaglutide. It is different to the Liraglutide TA 'secondary care by a specialist multidisciplinary tier 3 weight management service' . We have received feedback from our NICE associates that this was difficult to implement, and some services are not based in secondary care. Although this TA is less prescriptive it is something that may need addressing.	Thank you for your comment. The recommendations specify that semaglutide should be given within specialist weight management services, which may be in either primary or secondary care.

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66	Web commentator		Comments on the ACD: they have at least 1 weight-related comorbidity and: Does this include T2DM?	Thank you for your comment. The recommendations include people with at least 1 weight related comorbidity, which would include type 2 diabetes.
67	Web commentator		Has all of the relevant evidence been taken into account? No What is the evidence that a time limited use of semaglutide without tier 3 support will not cause weight liss? Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. I am not clear whether the evidence of a gp or hospital doctor using semaglutide will not cause weight loss Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Not all places have tier 3 service. Some places have tier 4 without tier 3. The insistence on tier 3 is a form of rationing that introduces post code lottery. Allowing use of semaglutide without the Tier restriction followed by gathering evidence systematically on the benefits and harms followed by a decision on Tier system is more logical and democratic.	Thank you for your comment. The committee was not aware of any evidence for use of semaglutide outside a specialist weight management service. It therefore was only able to make recommendations according to the evidence available which included semaglutide use alongside weight management support, diet and exercise. The committee also noted that the marketing authorisation for semaglutide specified that it should be used alongside diet and exercise, and that support for this is provided long term within specialist weight management services such as tier 3 services (see Final Appraisal Document [FAD] section 3.3). The committee was aware that tier 3 services are not available everywhere across the country, however it noted that specialist weight management services (such as tier 3 or tier 4 settings) are the only appropriate setting for semaglutide treatment (see FAD sections 3.2 and 3.3).
68	Web commentator		Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Thank you for your comment. The marketing authorisation does not allow use of semaglutide during pregnancy. No recommendations have been made specifically on use in pregnancy, but semaglutide should be used within its

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			Consideration has been given to the greater impact of obesity on individuals with disabilities and certain ethnic groups. Pregnant women should be prioritised for obesity management, given its recognised adverse effects on outcomes. This medication is however unlikely to be used during pregnancy.	marketing authorisation.
69	Web commentator		Are the recommendations sound and a suitable basis for guidance to the NHS? yes, They will need a lot of investment in Tier 3 services countrywide. There will need to be more dietitians and psychologists to support this. Many people will be eligible for this effective treatment and infrastructure will need to be paid for. There is no scope for existing services to absorb any more work Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I think so Are the recommendations sound and a suitable basis for guidance to the NHS? yes, Are the recommendations sound and a suitable basis for guidance to the NHS? I would agree Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Thank you for your comment. The implementation of the recommendations is outside the remit of this appraisal. The committee concluded that semaglutide should be used as part of a package of care provided in a specialist weight management service, based on the intervention used in the clinical trial, the marketing authorisation which specifies that semaglutide is given alongside diet and exercise and clinical expert opinion. The committee noted that tier 2 services are not long enough to establish treatment with semaglutide and do not include the support of a multidisciplinary team (Final Appraisal Document section 3.3). Therefore, it recommended that semaglutide should only be given within specialist weight management services.

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			GP in a Tier 2 setting should have the option of prescribing the same, if they have previously been to a Tier 4 service and was unable to proceed to surgery but remains a candidate for medical management; provided the GP in primary care is comfortable to do it or still has access for advice from a medical weight management specialist, in secondary care.	
70	Web commentator		The recommendation regarding use of semaglutide 'exceptionally' for some people with BMI 30 – 34.9 should be removed from the final recommendation. The word 'exceptionally' is unclear and there's no criteria as to when this should be applied. This recommendation should be removed or clarified further (i.e plus 2 or more metabolic or weight related complications which should be clearly defined). The draft recommendation doesn't cover the entirety of specialist weight management services but focuses on T3/4. The recommendation should clearly define whether this can be provided in 2ry care or even community based services. Furthermore, restricting prescribing through the use of a Tiered system approach is not appropriate as this may be a system which may hopefully be abandoned in the future and we move towards a more integrated care system. In STEP-1 trial, 86.4% of participants achieved >5 weight loss. Therefore, I feel that there should be no recommendation to stop treatment based on response after 6 months. It can be difficult to estimate accurately how long a patient has been on treatment and there are many parameters which can influence response within the NHS (delays with appointments, issues acquiring prescriptions on time etc). This recommendation is unreasonable as almost every patient on this treatment responds at least satisfactorily. Treatment discontinuation should be made on the basis of compliance to advice and engagement in the weight management programme.	Thank you for your comment. The term exceptionally has been removed from the recommendation. The recommendations have also been updated to refer to specialist weight management services (such as but not limited to tiers 3 and 4). Therefore, the recommendation does not restrict semaglutide use within the tier system. The committee noted that the marketing authorisation states that a decision on continuing treatment after 6 months without at least 5% weight loss should be made (see Final Appraisal Document section 3.11). The committee also heard from clinical experts that most people would not want to continue semaglutide after 6 months without a meaningful weight loss, especially considering the side effects associated with it. Therefore, it concluded that it was appropriate to include the stopping rule for people with less than 5% reduction in body weight at 6 months in the model. Due to the reasons described here, the recommendations have also been updated to also include this stopping rule.

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71			Has all the relevant evidence been taken into account? Yes we believe it has Are the summaries of the clinical and cost effectiveness reasonable interpretations of the evidence? We believe so however we have concern with maintaining the weight loss and the benefits plateau. Despite being more effective, as with other interventions the weight appears to return with the associated risks. There should be some work/focus on maintaining the weight loss and supporting further weight loss. Are the recommendations sound and a suitable basis for guidance for the NHS? Our thoughts are based on the challenges we would face as a Tier 3 service offering Semaglutide treatment as outlined in the NICE consultation document delivering especially that:- • the patient group in the trial referenced is not representative of current Leeds tier 3 population It is acknowledged in the consultation that the average BMI of patients in a tier 3 service is approx. 46, yet the average BMI of patients in the trial was 37.9, this is considerably lower than the average BMI of the Tier 3 caseload in Leeds. It is a concern that many patients with BMI<40 may be referred to tier 3 one the NICE TA is published. The current Tier 3 Service in Leeds is not set up to meet such demand.	Thank you for your comment. The committee was aware that weight is regained on average after semaglutide treatment is stopped. However, it is not within the remit of this appraisal to cover interventions on maintaining weight loss following discontinuation. The recommendation included people with at least 1 weight related comorbidity and a BMI of at least 35 kg/m2 or 30 to 35 kg/m2 based on specific criteria in NICE's clinical guideline on obesity: identification assessment and management. This is in line with current referral criteria for tier 3 services. The specification for a weight-related comorbidity is based on the clinical trial evidence, which included a population with a wide range of comorbidities. Therefore, the committee was unable to provide more specific recommendations on which weight-related comorbidities should be considered. Implementation of the recommendations from this technology appraisal in outside the remit of this appraisal, however the committee agreed that the current tiered system for obesity management is not ideal and suggested that this system should be reconsidered. It welcomed any review of NHS services for overweight and obesity (Final Appraisal Document [FAD] section 3.23). Further information on retreatment with

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			• There are no comorbidities stated It is acknowledged in the Consultation that there is variation in the comorbidities accepted for accessing tier 3. In the absence of comorbidities being specified by NICE it would be difficult to decline referrals for those with BMI<40 as many conditions such as low mood, joint pain could be claimed to be conditions linked to obesity. Unless the current list of accepted co-morbidities for access to Tier 3 in Leeds was maintained, referral numbers would be expected to rise significantly and the current service would be unable to meet demand • Semaglutide can be offered for up to 2 years The Consultation states that 2 years of treatment aligns with Tier 3 services . The Tier 3 service in Leeds is currently designed as a 12month pathway. I could not see outcomes reported from 12 months of Semaglutide treatment so the effectiveness of offering the treatment within the current 12 month pathway in Leeds is unclear. A service re-design of tier 3 in Leeds would be required to offer 2 years of Semaglutide treatment within tier 3 with consequent resourcing implications. • Access to Semaglutide for patients already in Tier 3 at the point the NICE TA comes into effect In practice, learning from experience in Leeds to comply with NICE TA 664 and offer Saxenda treatment to patients in Tier 3 who meet the specified criteria, it is a particular challenge to be able to deliver the new treatment to all eligible patients who are receiving care within the service at the point the NICE publication is launched. From my understanding of the consultation,	semaglutide has been included in section 3.14 of the FAD. The committee was aware that not all tier 3 services are accessed for 2 years (see FAD section 3.2). However, it noted that this is how long on average specialist weight management services can currently be accessed and that the company model was based on a course of treatment of no longer than 2 years, which is also in line with the clinical trial evidence currently available (see FAD section 3.12). The committee agreed that it could only make recommendations based on the current understanding of the structure of specialist weight management services, which it heard were not accessed for longer than 2 years. The committee acknowledged that retreatment might be appropriate for some people if they were eligible for treatment again according to the same starting criteria (see FAD section 3.14). Section 3.14 has been added to the FAD for clarification around retreatment.

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			most patients currently within the service would be eligible to be offered Semaglutide treatment. So for those patients nearing the end of their 12 months in the service their pathway would need to be extended for another 2 years. This would have considerable implications for service delivery in the medium term • Challenges with providing prescriptions from LTHT for injectable therapies Learning from prescribing Saxenda in Tier 3, a home delivery service has been required to be set up as this drug cannot be prescribed in primary care and needles and sharps bin etc need to be provided for patients • Repeat Semaglutide treatment will not be available The consultation states that re-referral to Tier 3 is unusual but this is not our experience. The difficulties faced by some patients due to life events etc lead them to discontinue on the Tier 3 pathway and they are re-referred at a later point. In practice, it would be a challenge for clinicians to be unable to re-offer Semaglutide during a subsequent Tier 3 episode of care. <u>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion orbelief, sexual orientation, age, gender reassignment, pregnancy and maternity?</u> no	

NICE National Institute for Health and Care Excellence

Semaglutide for managing overweight and obesity [ID3850]

Consultation on the appraisal consultation document – deadline for comments by 5pm on Tuesday 1 March 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Novo Nordisk Ltd.**]-
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Semaglutide for managing overweight and obesity [ID3850]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Novo Nordisk welcomes NICE's preliminary decision to recommend semaglutide 2.4mg for treatment in specialist weight management services (SWMS) recognising that the treatment is clinically and cost effective in a population with a high unmet need. We are grateful for the opportunity to provide our comments, which aim to improve the clarity of some aspects of the Appraisal Consultation Document.
2	The word 'exceptionally' in **Section 1.1** is imprecise and may infer that only some people with BMI 30-34.9 in SWMS are eligible for treatment. In Section 3.2 it is highlighted correctly that people with a BMI of 30 kg/m2 to 34.9 kg/m2 are already eligible for those services. Rapid research conducted with commissioners, chief pharmacists and other local payers indicated that the use of the word 'exceptionally' could result in clinicians having to provide supporting evidence of why a patient is considered exceptional which may require approval on a case by case basis via an exceptional case panel. To maintain consistency and clarity in the recommendation and to avoid adding to the administration burden, the word 'exceptionally' should be removed.
3	The reference to 'tier 3' in **Section 1.1** is inconsistent with the description of SWMS in Section 1.2. We suggest using the term 'specialist weight management services' in Section 1.1 to improve consistency while still reflecting the committee discussion. We suggest the following wording in **Section 1.1 and across the document:** *'a BMI of 30.0 kg/m2 to 34.9 kg/m2 for whom conventional treatment has been unsuccessful and who are suitable for referral to specialist weight management services according to NICE guidance on obesity*[1,2]*'*. 1. National Institute for Health and Care Excellence. Obesity: identification, assessment and management [CG189]. 2014. (Updated: 27 November 2014) Available at: https://www.nice.org.uk/guidance/cg189/resources/obesity-identification-assessment-and-management-pdf-35109821097925. Accessed: 25 February 2022. 2. National Institute for Health and Care Excellence. Obesity: clinical assessment and management (QS127). 2016. (Updated: May 2020) Available at: https://www.nice.org.uk/guidance/qs127/resources/obesity-clinical-assessment-and-management-pdf-75545363615173. Accessed: 25 February 2022.
4	We welcome the recommendation for treatment in SWMS with multidisciplinary input. To note, we heard at committee that a wide variety in service provision exists across the UK with some SWMS not being described formally as a tier 3 or tier 4 service, and with some provided in community care and others in a secondary care setting. To account for the variability of SWMS across the UK and not to further exacerbate any potential inequalities in service provision, we suggest changing the wording in **Section 1.2** to 'such as *but not limited to* tier 3 or tier 4 services'.
5	In **Section 1**, page 4 it is stated that 'It is appropriate to use semaglutide alongside intensive lifestyle interventions that are provided in specialist weight management services because this is in keeping with the clinical trial'. We would suggest removing the word 'intensive' because it is inconsistent with the license and the definition of lifestyle intervention in the STEP trials considered relevant for this appraisal (STEP 1, 2, 5, 8). Semaglutide is licensed to be used as an adjunct to a reduced-calorie diet and increased physical activity. The term 'intensive lifestyle interventions' is usually associated with intensive behavioural therapy as seen in the STEP 3 trial which, as the ERG and committee agreed, is not reflective of clinical practice in England.
6	In the title of **Section 3.19** it is stated that 'The ICERs for semaglutide compared with diet and exercise are uncertain, so a restricted version of the company's original target population is appropriate'. We would like to clarify that the company's original target population as noted on page 9 of the company submission is for people with a BMI of ≥ 30 mg/kg2 in the presence of at least one weight-related comorbidity for patients who are eligible for treatment within

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	specialist weight management services. It is therefore unclear how the recommended population differs.
7	In **Section 3.3**, page 8 the following is mentioned 'They also stated the importance of only offering semaglutide with these interventions because this was a requirement in the trial that showed favourable results. The clinical experts did not consider that semaglutide is a 'stand-alone' treatment.' We would like to clarify that the use of semaglutide 2.4mg as an adjunct to a reduced-calorie diet and increased physical activity is indicated by the treatment's MHRA license and is the main reason the treatment should not be used as a 'stand-alone'.
8	In **Section 3.6**, it is stated that 'The population in STEP 1 does not reflect the population distribution of overweight and obesity in clinical practice' and that the committee concluded 'the population in STEP 1 had a larger proportion of a high-risk population and did not reflect the population distribution of overweight and obesity in clinical practice'. We would like to request clarification on whether this sentence refers to the overall population seen in general clinical practice or the specialist weight management services population. Our understanding is that the statement applies to a general clinical practice and not SWMS where the treatment is positioned. We would propose the latter sentence to be followed by this text *'However the treatment is expected to be prescribed in specialist weight management services where the proportion of high-risk population is larger than in general clinical practice and more aligned with the population in STEP 1'*.
9	In **Section 3.7** it is stated that 'The clinical experts explained that if someone with type 2 diabetes needs specialist weight management then it would be appropriate for them to have treatment for obesity within a tier 3 service (or equivalent).' To avoid any confusion, we would propose changing the wording of this sentence to 'The clinical experts explained that if someone *with obesity* and type 2 diabetes needs specialist weight management then it would be appropriate for them to have treatment for obesity within a tier 3 service (or equivalent).' Moreover, this section should acknowledge that the company provided cost effectiveness estimates for this population using data from STEP 2.
10	In the title of **Section 3.10** it is noted that 'The company's model is only suitable for decision making for treatment in specialist weight management services'. This sentence is misleading as it is the data used in the model that makes the model suitable for decision making for treatment in specialist weight management services. The company submission is targeted to a population with a BMI of 30 or more plus 1 or more weight related comorbidity who are referred into a SWMS, consistent with the available data from the STEP programme.
11	In **Section 1.1**, we would suggest the text referring to different BMI criteria for specific ethnicities to be moved to a separate bullet point. This amendment should prevent any confusion on the BMI thresholds.
12	In the title of **Section 3.14** it is noted that 'The assumption that all people develop type 2 diabetes after a cardiovascular event is not correct'. This assumption refers only to people with non-diabetic hyperglycaemia. Additionally, this sentence is misleading because an assumption is required due to the unavailability of data. We point out that the alternative approach, i.e., assume that risk after a cardiovascular event is equivalent to patients with normal glucose control is also not correct, with the truth lying somewhere on this continuum. For accuracy, we would suggest replacing this sentence with *'The model assumes that all people with non-diabetic hyperglycaemia develop type 2 diabetes after a cardiovascular event'*. Additionally, in page 20 we would suggest replacing the word 'hyperglycaemia' with 'non-diabetic hyperglycaemia'.
13	Semaglutide is indicated for type 2 diabetes in different dosages. To avoid confusion, we would recommend replacing 'semaglutide' with 'semaglutide *2.4mg*' **across the document**.
14	In **Section 3.5** it is stated that 'the appropriate comparators for semaglutide were… liraglutide for people with a BMI of 35 kg/m2 or more, non-diabetic hyperglycaemia and a high risk of cardiovascular disease.' We suggest changing this to 'liraglutide 3mg *as an adjunct to lifestyle intervention*' to be consistent with the license for liraglutide 3mg (Saxenda®).

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15	In **Section 3.9** it is stated that 'liraglutide is the appropriate comparator for people with a BMI of 35kg/m2.'. We suggest changing this to '*liraglutide 3mg as an adjunct to lifestyle intervention'* to be consistent with the license for liraglutide 3mg (Saxenda®).
16	In **Section 3.17** it is stated that 'the ERG base case included some of the same assumptions as the company's with the following differences: the annual cost of sleep apnoea is £1,081 (compared with the company's assumption of £274)'. We would like to clarify that the company's assumption is £1,081 and the ERG assumption is £274.
17	In **Section 3.19**, the average BMI in STEP 1 is described incorrectly and inconsistently. The average BMI in STEP 1 was 39.7. Please update the document with the correct figure.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Prevention Team, NHS England and NHS Improvement (NHSE&I)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Name of commentator person completing form:	**Prevention Team, NHS England and NHS Improvement** The response below is an addendum to the submission by NHSE&I clinical advisor Gary McVeigh and the NHSE&I commercial directorate. NHS England and NHS Improvement (NHSE&I) has sought advice from the Obesity Tier 3 & 4 expert advisory group, chaired by Dr Jonathan Valabhji (National Clinical Director for Obesity and Diabetes) and agrees with the advice to the committee that the appropriate setting for follow-up of obese patients, suitable for semaglutide, would be within a specialist weight management (Tier 3) service. This ensures that semaglutide can be used within its license as an adjunct to a reduced-calorie diet and increased physical activity for weight management and ensures clear clinical governance arrangements are in place. NHSE&I disagrees with the proposed recommendation for semaglutide to be prescribed for a maximum duration of 2 years. The proposed time-limited access to treatment creates an artificial stopping point, not based on clinical evidence; once reached and treatment is stopped, there is evidence that patients will regain weight, as a result reducing the cost benefits of prescribing semaglutide. This will likely lead to some patients requesting re-referral into specialist weight management services, reducing cost-effectiveness further. NHSE&I does not nationally recommend a maximum duration that patients can access NHS obesity services. Applying a two-year limit to the prescribing of semaglutide could result in pressures on other services within the obesity pathway. We are aware that the committee has been informed that access to Tier 3 specialist weight management services is limited to 2 years; however, this does not reflect any national NHS guidance on the commissioning of specialist weight management services that we are aware of. The removal of the 2 year stopping rule would require remodelling for the delivery of the intervention. We insist that any significant change to the recommended eligibility criteria, such as alteration in the co-morbidities (e.g. making pre-diabetes a pre-requisite), undergoes a further round of public consultation. NHSE&I would like to reiterate the need to have full sight and approve any significant proposed changes to the TA recommendations for semaglutide.

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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1	The product license does not restrict treatment to 2 years for prescription of semalgutide. There is no national NHS direction on duration that patients have access to specialist weight management services; limiting the access to semaglutide to 2-years should be reassessed.
2	Following engagement with the NHSE&I Tier 3 & 4 Obesity Expert Advisory Group, the removal of the 2 year maximum time period for prescription of semaglutide was unanimously agreed. A 2 year time limited window for prescription creates an artificial deadline for patients to stop the treatment; [redacted] This will impact costs over time, leading to an increase – we ask that this is considered to reflect the cost effectiveness in the real world. We believe that if a treatment duration was longer than 2 years that the cost-effective value would be higher.
3	As a result of the removal of the 2 year stopping rule and a remodelling of the intervention, any significant further alterations to the recommended eligibility criteria of semaglutide should undergo an additional round of public consultation.
4	The current eligibility recommendations for semaglutide with a 2 year stopping rule would leave us out of line with the license and the rest of Europe.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of Physicians (RCP)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Advisory Group on Weight and Health and would like to comment as follows.
1	**We strongly disagree with the recommendation that semaglutide 2.4 mg be stopped after 2 years.** Obesity is recognised as a chronic relapsing progressing medical condition/disease like type 2 diabetes. Obesity is associated with multiple co-morbidities and reduced quality of life. Weight loss leads to improvement and/or remission of obesity-related comorbidities and improved quality of life. Importantly, the degree of improvement in health and quality of life depends upon the amount of weight loss, with greater improvements seen with greater weight loss. The improved efficacy of semaglutide 2.4 mg compared to currently available weight loss medications means that the health benefits and improvements in quality of life are greater. However, we know that when people stop taking any weight loss medication, they regain the weight lost, in keeping with obesity being a chronic medical condition. The findings from the STEP 4 trial show that participants regained the weight lost when they stopped semaglutide. This means that most people who will receive semaglutide for 2 years will then regain the weight lost and experience a worsening/relapse of their obesity-related comorbidities. This is also likely to have a negative impact upon their psychological well-being. We recommend that treatment is continued in patients who achieve weight loss and improvement in their health. However, if patients have to stop treatment at 2 years, then there needs to be clear guidance regarding restarting treatment e.g., regain of >5% body weight or recurrence of obesity-related complications.
2	Our experts question whether the committee considered the appropriateness of using semaglutide 2.4 mg in patient groups with a BMI between 30 and 34.9 who are required to lose weight prior to another surgical procedure in order to make this safer e.g., prior to surgery for endometrial cancer or other gynae procedures? It would also be helpful to know whether women who need to reach a BMI of ≤30 prior to being eligible for IVF would be included. People with serious mental illness are at specific increased risk of metabolic consequences of obesity and have more complications after bariatric surgery which is the only alternative currently available. Although there is evidence for liraglutide in counteracting the harmful effects of anti-psychotic medication we are not aware of any evidence for semaglutide specific to this population. Please can future recommendations consider this group separately – there is a trial ongoing the results of which should inform: Clozapine Obesity and Semaglutide Treatment (COaST). - qcmhr
3	The current NICE guideline regarding obesity management (2014) states that people with a BMI ≥35 with recent onset type 2 diabetes (T2DM) should have an expedited referral for assessment for bariatric surgery. This is based on the strong evidence that the likelihood of remission of type 2 diabetes after bariatric surgery is greatest when surgery is undertaken earlier.

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	Currently, few patients who should be offered bariatric surgery have this discussed with them. We are concerned that people with new onset T2DM and a BMI of ≥ 35 will be offered semaglutide 2.4 mg and not referred for assessment for bariatric surgery as per current NICE guidelines. At the moment there are no data regarding the long-term impact of semaglutide upon remission of T2DM. We suggest that this recommendation regarding referral for assessment for bariatric surgery is reiterated in this recommendation along with the fact that the long-term impact of semaglutide 2.4 mg upon T2DM remission is not known or that this is considered by the current guideline development group that is updating the obesity prevention and management guidelines.
5	We are concerned that the patchy provision of tier 3/tier 4 services will mean that there will be a postcode lottery with regards to accessing semaglutide 2.4 mg in the absence of additional funding for the establishment of new services. Currently, access to NICE TA approved liraglutide 3mg for weight management is limited via the proviso that this can only be prescribed by tier 3 services. Specialist weight management services already have a significant back log of patients waiting to be seen due to COVID-19. Without additional workforce expansion the implementation of this NICE TA will be difficult. At the moment there is little integration between Tier 2 and Tier 3 services. We suggest a shared-care model between specialist Tier 3 / Tier 4 services and Tier 2 /primary care weight management services. However, we appreciate that service structure is not the remit of NICE.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Obesity Group of the British Dietetic Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Section 1.1 Pg 3: These guidelines focus on reduced calorie intake and increased physical activity. NICE CG189 recommends multicomponent interventions i.e. inclusion of behaviour change alongside diet and activity. Multicomponent interventions are the treatment of choice. See recommendations 1.5.1 to 1.5.3 i.e. ensure weight management interventions include behaviour change interventions to increase physical activity or decrease calorie intake.
2	Section 1.1 Pg 3: We are pleased that the recommendation to use lower BMI cut-off points for specific ethnic groups is explicitly acknowledged, in light of the increased risks to these groups.
3	Section 1.3 Pg 3: We have concerns about the recommendation to use semaglutide for only two years. In one sense this suggest that obesity is a short-term condition, which it is not. However, we also feel that this recommendation lacks clarity e.g. can semaglutide be used repeatedly and if so, what is the recommendation around that?
4	Pg. 4. In place of 'Reverses prediabetes' we suggest 'helps people with prediabetes achieve a normal blood glucose more frequently'.
5	Pg 4: 'exceptionally with a BMI of 30-34.9kg/m^2'. There is a lack of clarity around what 'exceptionally' means in this context. Could specific examples be given for clarity?
6	Section 2.1 Pg 4: Could this be amended to 'as an adjunct to multicomponent interventions to increase physical activity and reduce calorie intake'?
7	Section 3.1 Pg 5: Obesity is recognised as a lifelong condition, yet semaglutide is only recommended for a maximum of two years. There appears to be discrepancy here which is unexplained.
8	Section 3.2 Pg 6: In relation to the statement that Tier 3 services are normally accessed for up to two years, we suggest that access to Tier 3 services (and the length of time they are accessed), is very variable, and 2 years is usual for Tier 2 services.
9	Section 3.3. Pg 7: We note that behavioural support was also offered within the STEP1 programme. We recommend that this is made explicit as an expectation of what would be part of the core offer of a care package.
10	Section 3.3 Pg 8: We agree that semaglutide should be offered alongside specialist weight management interventions. As per our earlier comment, we would like explicit mention of multicomponent interventions including behaviour change rather than a focus only on diet and physical activity, since behaviour change will be needed in both those areas.
11	Section 3.4 Pg 8: In relation to the population with a BMI of 30kg/m^2 and above, could we ask that (obese) in brackets is replaced with (obesity), since that is non-stigmatising language.
12	Section 3.4 Pg 9: In relation to 'Only exceptionally, referrals are made for people within this population, for example, when the person has a complex disease state or needs that cannot be managed adequately in tier 2', we agree with this but suggest that for clarity it is placed in the earlier recommendations.
13	Section 3.4 Pg 10: 'The committee concluded that the appropriate population for semaglutide comprises people at the highest risk for the adverse effects of obesity, which is the population eligible for specialist weight management services': We agree with and welcome this statement.
14	Section 3.6 Pg 11: In relation to STEP1, counselling is mentioned here for the first time. We would like this aspect highlighted elsewhere to ensure that those starting semaglutide are supported appropriately.
15	Section 3.6 Pg 12: 'The committee recognised that the highest risk population should be treated': We agree with and support this recommendation.

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16	Section 3.11 Pg 16: We agree with and welcome this stop rule. We think it is clear and sensible.
17	Section 3.12 Pg 16: 'and that there would be no retreatment': this is not included in the earlier guideline and we think it should be, for clarification. However, it is also not in line with the widespread recognition of obesity as a lifelong condition.
18	Section 3.12 Pg 16: 'The clinical experts explained that some people who have regained weight after weight loss with semaglutide may wish to take it again'. We agree with this statement and would encourage this to be reconsidered. The impact of weight regain and potential feelings of failure are likely to be substantial in those living with overweight or obesity. This is of concern particularly given the risk of worse mental health in this group.
19	Section 3.12 Pg 17: In relation to the 2 years of semaglutide treatment and the alignment with Tier 3 services, at least some Tier 3 services are commissioned only for one year. would patients accessing those services have to stop taking semagluide if they are discharged before 2 years?
20	Section 3.13 Pg 17: In relation to the assumption that 'weight would be in line with what it would be in the average population after 5 years of only diet and exercise', we suggest that this negates the emotional impact of weight regain in those living with overweight or obesity..
21	Section 3.17 Pg 20: We disagree with the following recommendations, for reasons already outlined: • a maximum treatment duration of 2 years (see section 3.12) • no retreatment throughout the full time horizon of the model (see section 3.12)

Insert extra rows as needed

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- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Semaglutide for managing overweight and obesity [ID3850]

Consultation on the appraisal consultation document – deadline for comments by 5pm on Tuesday 1 March 2022. Please submit via NICE Docs.

NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No disclosures.**
Name of commentator person completing form:	Beverley Burbridge

Comment number	Comments

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Semaglutide treatment is going to be limited for a treatment period of 2 years, this needs to be a lifelong treatment.
2	People that have had bariatric surgery and a start BMI of >40, surely the damage has been done to the heart so Semaglutide could be issued to people that have a current BMI of 27-30 as a maintenance dose. Many people find it difficult even after surgery to maintain.
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Insert extra rows as needed

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NICE, its officers or advisory committees.

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Name	Ken Clare
Role	Patient expert
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Yes but some concerns about 2 year duration of treatment Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]NHSE
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]N0NE

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Name of commentator person completing form:	[**Insert your name here**]Professor Gary McVeigh; clinical advisor NHSE NHSE recognises advice to committee that the appropriate setting for follow-up of obese patients, suitable for Semaglutide, would be within a specialist weight management (Tier 3) service. NHSE also recognise advice to the committee has been that patients can remain in Tier 3 services for a maximum of 2 years when responders to Semaglutide will then be required to stop the drug and will be discharged from the service with no further access to treatment. NHSE has expressed the view that it is inappropriate to use QRISK-3 to predict 10-year risk for adverse cardiovascular outcomes for a time-limited use of Semaglutide when regain in weight and loss of benefit on weight associated surrogate cardiovascular risk factors is inevitable. NHSE notes the recent publication of real-world data from a UK population that was not available to committee at the time of approval of Liraglutide. These data provide objective real-world quantification of the effects of intentional weight loss on obesity related CVD risk factors (Type 2 diabetes mellitus, hypertension and dyslipidaemia) and CV outcomes (atrial fibrillation, heart failure, unstable angina and myocardial infarction). Using data from CPRD-GOLD database cohorts were defined as having stable weight (-5% to +5%) or weight loss (- 25% to -10%). The stable weight cohort comprised 523,138 individuals and the weight loss cohort 48,823 individuals. The median age at the beginning of the follow-up period was 55 years and the follow-up time was median 6.3 years. The median weight loss was 13% compared with controls and the lower BMI , maintained over time, was associated with significant reductions in T2DM, blood pressure and improvements in dyslipidaemia. The beneficial impact on surrogate risk factors for CV disease were not associated with any benefit in any of the CV outcomes of atrial fibrillation, heart failure, unstable angina or myocardial infarction. NHSE note the very large sample size and the prolonged duration of follow-up of the weight loss and stable weight cohorts. Importantly, NHSE note the baseline 10-year risk for future myocardial infarction/stroke, based on QRISK-3, in the real-world cohort is approximately x3 that for the population included in the STEP-1 trial, due largely because of the older age at the beginning of follow-up and a greater percentage of male participants. Despite being at greater risk for adverse CV outcomes, no such signal was evident in the real-world weight loss participants compared with the control participants. NHSE is not aware of any CV outcome trial planned for a population similar to that in the STEP-1 trial and suspects such a trial will never be undertaken due to logistical and other challenges involved in setting up such a trial.

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	All patients responding to Semaglutide will be required to stop the drug and will be discharged from the specialist weight management service with no further access to the drug.
2	The analysis implies it is appropriate to use QRISK-3 to predict the 10-year risk for MI/CVA using a time-limited (maximum -2 years) administration of Semaglutide when weight regain is inevitable and there is loss of effect on the surrogate CV risk factors. QRISK-3 should not be used in this way and the NHSE view is that this analysis is inappropriate. In addition, NHSE notes the potential for adverse mental and physical outcomes for responders to the medicine who simultaneously lose access to Semaglutide and access to SWMS at 2 years.
3	Given the real-world evidence, indicating no CV outcome benefit in a higher risk population for adverse CV outcomes compared with the participants in the STEP-1 trial, NHSE believes there is no evidence to support any CV outcome benefit for a time-limited use of the drug. Even if the drug were to be continued and patients continue to respond, current evidence suggests that no benefit on CV outcomes can be assumed, at least up to 7 years with maintenance of weight loss. Assuming no CV benefit markedly increases the ICER with time-limited (maximum-2 years) use of the drug.
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Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are the recommendations sound and a suitable basis for guidance to the NHS?

Overall the ASO welcomes the NICE appraisal and feel that it will benefit many patients with obesity in view of the wide eligibility criteria.

The concerns raised by the ASO Trustees are summarised below:
1. It is unusual for a chronic disease to be treated for 2 years only. Medications for other chronic conditions, some of them expensive, are continued for life (e.g. dyslipidaemia with PCSK9 inhibitors or inflammatory conditions with biological therapies). The two year cutoff may make cost effectiveness sense but not clinical sense. Guidance on what the options for patients are after the 2 year course would be very useful.

2. "exceptionally, a BMI of 30.0 kg/m2 to 34.9 kg/m2": This eligibility criterion is vague. What does exceptionally actually mean in practice?

3. In practice, it is not clear how this should be funded.
a. If the medication is started in a hospital tier 3 setting, would it be possible for the prescriptions to be continued by primary care (a model similar to diabetes care) or would prescriptions and therefore associated costs remain in secondary care?
b. It would be useful if the appraisal could clarify whether the medication can be prescribed in a community tier 3 setting.

4. Concerns were raised regarding the implementation of the guidance with the available resources in tier 3/4 settings. The lack of staff needed to initiate the medication and conduct the follow-up will mean that long waiting lists will be formed very rapidly.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Only 40-50% of the country has tier 3 service provision, thus this guidance will disadvantage the other half of the population that do not have these services available to them. This raises the question as to whether the medication should be routinely prescribed by primary care as part of a tier 2 service.

Name	
Role	
Other role	
Organisation	
Location	
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Comments on the ACD:

Any stopping criteria should be driven my medical need (e.g. evidence of toxicity with repeated dosing) or best-available evidence (e.g. the drug stops working). In the case of semaglutide, we have high-quality evidence that it is neither toxic nor ineffective long-term. It is clinically appropriate therefore to continue long-term at least in a proportion of the population who are not eligible for surgery or cannot sustain weight loss with lifestyle modification.
NICE must review the cost-effectiveness of continued treatment as this will happen in clinical practice.

As we anticipate major implementation challenges with the stopping rule requirement of this TA, a proportion of patients will continue treatment long-term (as they continue to benefit). Under the assumption that the decision rule introduced by the manufacturer exists only because without it, the drug is not cost-effective, NICE must acknowledge that they are committing the NHS to prescribe a drug which is not cost-effective by stealth.

Semaglutide is a chronic condition. Whilst a proportion of patients be able to discontinue treatment (after successful lifestyle modification, or surgery) a not insignificant proportion of patients will require lifelong treatment. The requirement for life long treatment is is acknowledged by the patient experts and the Committee in Section 3.12. A stopping rule for all patients is not clinically appropriate therefore will have major implementation challenges for the NHS.

Novo Nordisk has a track record of introducing clinically unjustifiably stopping rules that are not adhered to in clinical practice. Liraglutide 1.2mg was given a positive TA for type 2 diabetes as NICE found the drug to be cost-effective if a major improvement in both HbA1c AND weight were seen at 6 months. In clinical practice however a significant proportion patients experienced either one or the other of these benefits. The TA required that liraglutide is discontinued for these patients are (as both benefits were not observed) however in practice this rarely happened as patients could see improvement in their clinical condition. Predictable and significant non-compliance to this stopping rule effectively meant that NICE introduced a drug in NHS practice which was not cost-effective. NICE must reconsider their approach to stopping rules.
We know it is clinically appropriate for patient to continue semaglutide drug long-term, therefore NICE must assess the cost-effectiveness of this approach.

We acknowledge that the same decision rule as exists for liraglutide 3 mg however it is not acceptable for NICE to continue with this error of judgement. This stopping rule should be removed and the cost-effectiveness of life-long semaglutide considered.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No. NICE is endorsing a 2 year treatment course for a chronic condition; this approach is not evidence based and has major implementation challenges. The 2 year decision rule is a feature of the economic analysis introduced by the manufacturer to make the drug look more cost-effective than it is. NICE should review the cost-effectiveness of long-term treatment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No. NICE is endorsing a 2 year treatment course for a chronic condition; this has major implementation challenges. Insufficient advice is provided for the significant proportion of patients who will regain weight after the 2 year treatment window.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No

Name	

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We welcome the addition of Semaglutide as a proven effective treatment choice for people living with obesity and overweight. The current pharmacological treatment options are limited to Orlistat - which is poorly tolerated in many people and rarely used - and Liraglutide for those with a BMI over 35kg/m2 so the addition of Semaglutide offers greater choice to more people living with this condition who want to lose weight.

Although the submitted trial data did not include people with type 2 diabetes, the summaries highlight the benefits of this treatment for this group. We feel this is much-needed given what we know about the effectiveness of the treatment and increasing prevalence of type 2 diabetes in the population. Our statistics show that the prevalence of diabetes has more than doubled in the last 15 years with 4.9 million now living with the condition in the UK and 90% of these having type 2 diabetes. A further 13.6 million people are at an increased risk of developing type 2 diabetes. Obesity is the most significant modifiable risk factor and accounts for as much as 85% of the overall risk of developing type 2 diabetes; it is also associated with difficulties managing blood glucose levels and an increased risk of complications in those already diagnosed. Semaglutide is therefore an important

step in mitigating this and supporting people with or at risk of type 2 diabetes to lose weight improve their underlying health.

Furthermore, Semaglutide is administered as a once-weekly injection compared to Liraglutide which is a once-daily injection so it is appealing to many people who prefer less injections for various reasons such as needle phobia.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

With regard to the expected weight re-gain after discontinuation of semaglutide: The findings of the paper: Le Roux et al. Lancet 2017 (showing the 3 year outcomes of the SCALE obesity pre-diabetes trial) demonstrated significant rapid weight regain in the first 12 weeks after stopping liraglutide. The drug was stopped at week 160 in this trial, weight gain at week 172 is reported. Extrapolating from the published data and graphs in that paper it is reasonable to assume that all the weight advantage of liraglutide would be lost within 6-12 months of discontinuation. It is reasonable to assume that semaglutide discontinuation would follow a similar clinical course and that all of the weight advantage would be lost over period of 6-12 months. This evidence does not appear to have been considered in section 3.13. It should be taken into account.

Reference:
Le Roux et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017 Apr 8;389(10077):1399-1409.

Patients who have had previous bariatric surgery and weight regain should be excluded from these recommendations because they represent an entirely different cohort of patient as compared to surgically naive patients.
The assumptions of the cost-effectiveness analysis do not apply to the post-surgical group.

Patients who have already had bariatric surgery are at a different phase of their obesity journey. The majority will have had prolonged severe morbid obesity in the past and may have already developed complications related to obesity. The Markov state-transition cohort model being used describes 11 health states, but the patients who have previously had morbid obesity, bariatric surgery weight loss and then weight-regain are not comparable to the health states used in the model. Their metabolic risk profile, complication risk and service use is not comparable to the group that are using semaglutide as a relatively early intervention for obesity.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

It should include patients experiencing a weight gain due to taking SSRI/Anti psychotic medication. Particularly as this weight gain is largely unavoidable and can contribute to levels of non concordance with medication for this reason

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

As above

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account? Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Not entirely. Please refer to specific criticisms on relevant sections of the document below.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Not entirely. Please refer to specific criticisms on relevant sections of the document below.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Response to NICE Appraisal consultation document on 'Semaglutide for managing overweight and obesity'

Dr Harriet Feldman BA (Cantab) PhD (UCL) BM BCh (Oxon)
Academic Clinical Fellow
University Dept. of Psychiatry, University of Oxford

Dr Valeria Frighi MD (Rome) MRCP (London)
Senior Clinical Research Fellow and Honorary Consultant in Endocrinology and Diabetes
University Dept. of Psychiatry, University of Oxford

We are writing to raise concerns that the consultation document as it stands unlawfully discriminates against people with severe mental illness (SMI).

SMI is defined as "psychological problems that are often so debilitating that patients' ability to engage in functional and occupational activities is severely impaired". Schizophrenia and bipolar disorder are examples of SMI. People with SMI experience substantial health inequalities and have poorer physical health than those without SMI(1). Notably, rates of obesity are 80% higher in people with SMI.

People with SMI are considered to have a disability under the Equality Act 2010. Therefore, this guidance needs to consider their particular needs. In its current form, this guidance will substantially limit the access of people with SMI to treatment with semaglutide by reason of their disability, by both direct and indirect discrimination. As such, we believe it may unlawfully discriminate against this group.

The main barrier to access to this treatment for people with SMI is the requirement that semaglutide be provided only within a Tier 3 obesity service. People with SMI are discriminated against by Tier 3 services both directly and indirectly.

There is evidence of direct discrimination against people with severe mental illness by Tier 3 obesity services. For example, a simple Google search of 'tier 3 obesity services' shows evidence of explicit exclusion of this group in all three of the first three returned referral criteria:

- "Patients who have active mental health problems, i.e. are under the care of the community mental health teams or in-patient care, should not be referred to the Obesity Management Programme"(2)
- Exclusion criteria include "Clients with an unstable psychiatric disorder"(3)
- Exclusion criteria include "Active psychosis"(4)

In addition to the direct discrimination by explicit exclusion of patients with SMI, there is also indirect discrimination. Most Tier 3 services demand a high level of active engagement by patients who are referred to them, and many require previous substantial self-directed efforts at weight loss before offering an intervention. People with SMI often have specific deficits such as avolition (lack of motivation to perform even rewarding or pleasurable activities) and lack of executive control (the ability to plan and carry out a complex series of actions). Both of these deficits mean that people with SMI would struggle to meet these criteria more than a person without SMI, due to their disability.
This discrimination might be legal under the Equality Act, as Tier 3 services as they currently stand may lack the necessary skills to work effectively with this group. However, it is not clear where this group can access specialist weight management support – which may leave the NHS in breach of its duties under the Equality Act 2010. Some, but not all(5), secondary care mental health services do provide advice and management of physical health, including some lifestyle advice for weight management, to patients with severe mental illness. However, if this is felt to be equivalent to a Tier 3 service negating the need for specialist provision, then semaglutide would need to be available within this service.

It is particularly unjust to limit access to a weight loss intervention for people with SMI. Much of the weight gain in SMI is iatrogenic. Most patients with SMI will be treated with a second-generation antipsychotic medication such as olanzapine, risperidone and clozapine. Patients with SMI are likely to take these medications for life. Weight gain is an almost universal side effect from these medications, as well as more widespread metabolic derangement which leaves people with SMI at elevated risk of most of the complications of obesity. Medication-related weight gain is a key driver of non-adherence with treatment for severe mental illness such as schizophrenia(6), and stopping or reducing medication often results in relapse of illness and the need for inpatient treatment – which can be devastating for the individual as well as costly to the NHS.

Situating access to semaglutide within Tier 3 obesity services could be seen as a strategy for demand management. In people without SMI, this is justifiable; obesity for most people is a complex social and behavioural problem and effective strategies for behaviour change at the national level are preferable solutions to expensive pharmaceuticals. However, for people with SMI, obesity is much more likely to have a medical cause – as a medication side effect – rendering policy change less effective and pharmaceutical management more appropriate. Tier 3 services might also be inappropriate for people with SMI because there is strong evidence – from the STEPWISE trial – that even intensive diet and lifestyle programs have zero impact on weight in this group(7).

Pharmacological management of weight gain therefore looks increasingly important for people with SMI. Liraglutide has been trialled in people with SMI, with positive results – around 6kg of weight loss with treatment(8,9), maintained at 1 year(10). This weight loss is clinically significant, and importantly was achieved without a concomitant intensive diet and exercise intervention. A major barrier to recruitment in one trial was the need to self-administer liraglutide as a daily injection – meaning semaglutide is a far more feasible treatment in this group.

There are outstanding questions about the cost-effectiveness of semaglutide in people with SMI. However, there is reason to believe that prevention of co-morbidity associated with obesity may be more cost-effective in people with SMI.

People with SMI are less able to self-manage diabetes effectively(11) and more likely to suffer complications(12,13). Both inpatient and outpatient costs are increased after MI for patients with SMI(14), and mental illness increases the likelihood of needing institutional care after stroke 6-fold(15).

In conclusion, we believe that semaglutide should be offered to people with SMI via secondary care mental health services, and not within specialist weight management services. Failure to do so means direct discrimination against this group, entrenching the health inequalities which mean people with SMI die 10-20 years younger. Weight gain in people with SMI has been shown to be iatrogenic, not amenable to lifestyle change by the individual, and at least partly reversible by the daily use of liraglutide, which is similar to but less effective and convenient than semaglutide(16). We have a particularly great responsibility to offer individuals with SMI the same chance at the best possible treatment that is being given to the rest of the population.

1 Public Health England. Severe mental illness (SMI) and physical health inequalities: briefing. 27 September 2018
2 https://www.valeofyorkccg.nhs.uk/rss/home/general-surgery/tier-3-obesity-management-service/ accessed 18/2/2022
3 NHS Dorset Clinical Commissioning Group. Obesity and Tier 3 Weight Management Programme Criteria Based Access Protocol. Accessed 18/2/2022
4 https://westessexccg.nhs.uk/health-professionals/referrals-pathways-and-guidance/diabetes/diabetes-prevention-and-support-services/weight-management-1/tier-3-weight-management-service - referral form downloaded 18/2/2022
5 Swaby, L., Holt, R., Gossage-Worrall, R., & Hind, D. (2019). Provision of weight loss programmes and their influence on weight after 1 year: Follow-up survey of usual care in the STEPWISE study. BJPsych Bulletin, 43(5), 245-246. doi:10.1192/bjb.2019.59
6 Wong, M., Chen, E., Lui, S., & Tso, S. (2011). Medication adherence and subjective weight perception in patients with first-episode psychotic disorder. Clinical schizophrenia & related psychoses, 5(3), 135-141.
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Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:
Thank you. It is great that Semaglutide will be available to people with obesity on the NHS. However, I feel there is a need for more clarity around a few points:

1. What would you define as obesity-related comorbidity?

2. Will people post bariatric surgery be eligible for Semaglutide? Has a cost-benefit analysis been performed?

3. Including people with BMI 30-35 will lead to a big shift in the number of referrals from this cohort and the patient population in a tier-3 weight management service. This will have big implications on demand and service delivery; this needs to be taken into consideration.
Saying "exceptionally" and then referring to NICE clinical guidelines on obesity, which say "consider referral to tier-3 if: conventional treatment has been unsuccessful". That means almost everyone will be eligible and it is not exceptional. Currently this cohort is not seen in a tier-3 service mainly because they are not asking for the referral. With the option of Semaglutide, more people will be asking to be referred to WMS. There is nothing wrong with that, but without the infrastructure to support this model, there will be lots of tension and disappointment for everyone involved.

4. More clarity in the recommendation around re-treatment with Semaglutide is needed.
Has all of the relevant evidence been taken into account? Yes Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes Are the recommendations sound and a suitable basis for guidance to the NHS? Yes Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Yes

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

Semaglutide will be welcome in the Tier 3 service and the BMI targets are appropriate and in line with the referral criteria to the Tier 3 service. There is a further need to specify assessment for suitability/expectation management and monitoring of the effect of therapy for further prescription.

Has all of the relevant evidence been taken into account?

Existing evidence has been considered, however the lack of evidence in certain areas should equally be acknowledged. This concerns the use of GLP-1 in treating eating disorders with and without psychological therapies (and respective engagement in combination), clinical depression, GLP-1 use in bariatric workup and comparison with surgical outcomes.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

There are reasonable within the limitations of research not representing real life complexities and with the lack of evidence regards long term use on weight loss. It would be beneficial for the clinicians to know when Semaglutide is no longer considered (cost)-effective and to be discontinued.

Semaglutide will be welcome in the Tier 3 service and the BMI targets are appropriate and in line with the referral criteria to the Tier 3 service. These services may work in slightly different pathways, e.g. some may work more towards conservative management, whilst others work predominantly towards pre-surgical workup. Part of both is an evaluation of eating pathology and mental health needs which have a high prevalence in obesity populations, especially in those with higher BMIs. Externalising eating behaviour will be most amenable to target with drugs, whilst emotional eating and binge eating will require psychological support. Patients however may be referred and expect a 'drug therapy fix' and/or (plus additional surgical fix) and opt out of recommended psychological therapies. Evidence so far was unable to address these co-morbidities and research studies rarely recruit patients with mental health problems. I propose monitoring of the engagement with lifestyle change in addition to ongoing prescribing such as proposed with Saxenda. In addition, patients should choose whether to opt GLP-1 analogues or chose the surgical pathway as the two in parallel have 1) not been tested, alias no evidence, 2) it will not be possible to assess surgical readiness regards of underlying eating pathology such as restraint eating behaviours which underlie eating disorders. Latter may resurface after surgery and compromise long term success beyond 2 years after surgery. Thus, I would like to see GLP-1 treatments part of a separate referral/ Tier 3 treatment pathway to the bariatric surgical pathway with clear expectation management at the outset.
In summary, it is unclear when to use GLP-1 analogues versus prepare patients to bariatric surgery and whether GLP-1 analogues should be continued if not showing any effect on weight loss. Inclusion of a discontinuation guideline within the 2 years of therapy is needed.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? No concerns

Name	
Role	
Other role	
Organisation	
Location	
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Comments on the ACD:	

Are the recommendations sound and a suitable basis for guidance to the NHS?
Rec 1.2
There is potential for confusion with the criteria for prescribing semaglutide. It is different to the Liraglutide TA 'secondary care by a specialist multidisciplinary tier 3 weight management service' . We have received feedback from our NICE associates that this was difficult to implement, and some services are not based in secondary care. Although this TA is less prescriptive it is something that may need addressing.

Name	
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Other role	
Organisation	
Location	
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Comments on the ACD: they have at least 1 weight-related comorbidity and: **Does this include T2DM?**	

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?
No
What is the evidence that a time limited use of semaglutide without tier 3 support will not cause weight liss?

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?
No. I am not clear whether the evidence of a gp or hospital doctor using semaglutide will not cause weight loss

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not all places have tier 3 service. Some places have tier 4 without tier 3. The insistence on tier 3 is a form of rationing that introduces post code lottery. Allowing use of semaglutide without the Tier restriction followed by gathering evidence systematically on the benefits and harms followed by a decision on Tier system is more logical and democratic.

Name	
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Other role	
Organisation	
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Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Consideration has been given to the greater impact of obesity on individuals with disabilities and certain ethnic groups. Pregnant women should be prioritised for obesity management, given its recognised adverse effects on outcomes. This medication is however unlikely to be used during pregnancy.	

Name	
Role	
Other role	
Organisation	
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Comments on the ACD:	
Are the recommendations sound and a suitable basis for guidance to the NHS? yes, They will need a lot of investment in Tier 3 services countrywide. There will need to be more dietitians and psychologists to support this. Many people will be eligible for this effective treatment and infrastructure will need to be paid for. There is no scope for existing services to absorb any more work	

Name	
Role	
Other role	
Organisation	

Location	
Conflict	
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Comments on the ACD:

They will need a lot of investment in Tier 3 services countrywide. There will need to be more dietitians and psychologists to support this. Many people will be eligible for this effective treatment and infrastructure will need to be paid for. There is no scope for existing services to absorb any more work

Has all of the relevant evidence been taken into account? Yes

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? I think so

Are the recommendations sound and a suitable basis for guidance to the NHS?

yes,

Are the recommendations sound and a suitable basis for guidance to the NHS?
I would agree

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

GP in a Tier 2 setting should have the option of prescribing the same, if they have previously been to a Tier 4 service and was unable to proceed to surgery but remains a candidate for medical management; provided the GP in primary care is comfortable to do it or still has access for advice from a medical weight management specialist, in secondary care.

Name	
Role	
Other role	
Organisation	
Location	
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Comments on the ACD:

<u>Has all the relevant evidence been taken into account?</u>

Yes we believe it has

<u>Are the summaries of the clinical and cost effectiveness reasonable interpretations of the evidence?</u>

We believe so however we have concern with maintaining the weight loss and the benefits plateau. Despite being more effective, as with other interventions the weight appears to return with the associated risks. There should be some work/focus on maintaining the weight loss and supporting further weight loss.

Are the recommendations sound and a suitable basis for guidance for the NHS?

Our thoughts are based on the challenges we would face as a Tier 3 service offering Semaglutide treatment as outlined in the NICE consultation document delivering especially that:-

- the patient group in the trial referenced is not representative of current Leeds tier 3 population

  It is acknowledged in the consultation that the average BMI of patients in a tier 3 service is approx. 46, yet the average BMI of patients in the trial was 37.9, this is considerably lower than the average BMI of the Tier 3 caseload in Leeds. It is a concern that many patients with BMI<40 may be referred to tier 3 one the NICE TA is published. The current Tier 3 Service in Leeds is not set up to meet such demand.

- There are no comorbidities stated

  It is acknowledged in the Consultation that there is variation in the comorbidities accepted for accessing tier 3. In the absence of comorbidities being specified by NICE it would be difficult to decline referrals for those with BMI<40 as many conditions such as low mood, joint pain could be claimed to be conditions linked to obesity. Unless the current list of accepted co-morbidities for access to Tier 3 in Leeds was maintained, referral numbers would be expected to rise significantly and the current service would be unable to meet demand

- Semaglutide can be offered for up to 2 years

  The Consultation states that 2 years of treatment aligns with Tier 3 services . The Tier 3 service in Leeds is currently designed as a 12month pathway. I could not see outcomes reported from 12 months of Semaglutide treatment so the effectiveness of offering the treatment within the current 12 month pathway in Leeds is unclear. A service re-design of tier 3 in Leeds would be required to offer 2 years of Semaglutide treatment within tier 3 with consequent resourcing implications.

- Access to Semaglutide for patients already in Tier 3 at the point the NICE TA comes into effect

  In practice, learning from experience in Leeds to comply with NICE TA 664 and offer Saxenda treatment to patients in Tier 3 who meet the specified criteria, it is a particular challenge to be able to deliver the new treatment to all eligible patients who are receiving care within the service at the point the NICE publication is launched. From my understanding of the consultation,

most patients currently within the service would be eligible to be offered Semaglutide treatment. So for those patients nearing the end of their 12 months in the service their pathway would need to be extended for another 2 years. This would have considerable implications for service delivery in the medium term

- Challenges with providing prescriptions from LTHT for injectable therapies

  Learning from prescribing Saxenda in Tier 3, a home delivery service has been required to be set up as this drug cannot be prescribed in primary care and needles and sharps bin etc need to be provided for patients

- Repeat Semaglutide treatment will not be available

  The consultation states that re-referral to Tier 3 is unusual but this is not our experience. The difficulties faced by some patients due to life events etc lead them to discontinue on the Tier 3 pathway and they are re-referred at a later point. In practice, it would be a challenge for clinicians to be unable to re-offer Semaglutide during a subsequent Tier 3 episode of care.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion orbelief, sexual orientation, age, gender reassignment, pregnancy and maternity?

no

Do you or the organisation you represent have any links with the tobacco industry? No

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Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Semaglutide for managing overweight and obesity

Evidence Review Group's critique of the company's response to the appraisal consultation document (March 2022)

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Date completed	7 March 2022

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1. Introduction

This document is the Evidence Review Group's (ERG) critique of the response by the company, Novo Nordisk Ltd, to the National Institute for Health and Care Excellence (NICE) appraisal consultation document (ACD) (Issue date: February 2022) for the technology appraisal on semaglutide for managing overweight and obesity [ID3850]. The ERG received the company's ACD response form on the 1st March 2022.

The ERG notes that most of the company's comments in response to the ACD relate to the wording of some aspects of the document. We therefore have not provided a critique of the majority of the company's comments, but we have identified four where we believed that clarification and a response from the ERG would be beneficial. These are: comments 10, 12, 16 and 17. We provide our responses in section 2.

In addition to providing a critique of the company's comments, NICE asked the ERG to include commentary here on evidence one consultee submitted about the potential trajectory of weight regain over time after discontinuation of semaglutide. We comment on this evidence in section 3.1.

The ERG also received consultation comments from NHS England (NHSE). NSHE disagreed with the company's use of QRisk-3 equations to predict cardiovascular events in the economic model. NHSE also noted a lack of evidence on the longer-term cardiovascular outcome benefits of treatment. We comment on these issues in sections 3.2 and 3.3. In section 3.3, we have also provided a scenario analysis where we have excluded complications due to acute coronary syndrome and stroke from the model, to explore the effect of excluding benefits for cardiovascular disease (CVD) on the incremental cost-effectiveness ratio (ICER).

2. ERG critique of company ACD comments

2.1. Comment 10: ACD wording relating to the suitability of the economic model for decision making for treatment in specialist weight management services

The company comments that the wording for section 3.10 is misleading as it is the data used in the model that makes the model suitable for decision making for treatment in specialist weight management services.

We agree with the company's comment. The reason the economic model is only suitable for specialist weight management services is due to the data available and presented by the company (such as for treatment effectiveness) and it is unclear how relevant these data would be for other settings.

2.2. Comment 12: ACD wording relating to the economic model assumption about who develops type 2 diabetes after a cardiovascular event

The company comments that the title of section 3.14 ("The assumption that all people develop type 2 diabetes after a cardiovascular event is not correct", ACD, p. 17) is misleading as the development of type 2 diabetes after a cardiovascular event assumption refers to patients with non-diabetic hyperglycaemia, rather than all patients. The ERG confirms that the assumption used in the model that people develop T2D after a cardiovascular event only applies to people with non-diabetic hyperglycaemia.

2.3. Comment 16: The ERG's sleep apnoea cost assumption

The company comments that the costs of sleep apnoea have been incorrectly attributed to the ERG and the company in section 3.17 of the ACD. We agree with the company's comment and confirm that the cost of sleep apnoea was assumed to be £1,051 by the company and £274 by the ERG.

2.4. Comment 17: ACD description of the average BMI in the STEP 1 trial

The company comment that the average BMI in the STEP 1 trial is incorrectly and inconsistently reported in section 3.19. They state that the average BMI in STEP 1 was 39.7.

The ERG notes that the average BMI in the STEP 1 study is 37.9, as reported in Table 5 of the company submission for the full analysis dataset. In the population used for the company base case analysis (BMI ≥ 30 plus one co-morbidity population), the average BMI is 38.7.

3. ERG critique of other consultee comments

3.1. Expected weight re-gain after discontinuation of semaglutide

One consultee highlighted a study by Le Roux et al[1] with regard to the expected weight re-gain after discontinuation of treatment. This study reports the three-year outcomes of the SCALE Obesity and Prediabetes trial. The consultee commented the study demonstrated significant rapid weight regain in the first 12 weeks after stopping liraglutide (weeks 160-

172). The consultee commented that extrapolating from this 12-week period, it would be reasonable to assume that all the weight advantage of liraglutide would be lost within 6-12 months of discontinuation and that this weight re-gain would be similar for semaglutide.

The ERG suggests caution in extrapolating the weight re-gain at 12 weeks to longer periods, such as 6-12 months. We consider that the STEP 4 trial (Rubino et al.[2]) provides a better indication of the likely weight re-gain after semaglutide discontinuation. The STEP 4 trial investigated the effect of continuing vs withdrawing treatment with semaglutide. Patients received 20 weeks treatment with semaglutide 2.4mg and then were randomised to continuing semaglutide or placebo. Patients were followed for a further 48 weeks. All participants received a lifestyle intervention, including a reduced-calorie diet and increased physical activity, for the duration of the trial.

The STEP 4 trial (Rubino et al.[2]) results show that, on average, patients who ceased treatment with semaglutide and switched to placebo did not regain all the weight that they had lost within one year – we refer the reader to Figure 2 of Rubino et al.,[2] which shows trends over time in the mean percent change in body weight for each trial arm during the 68 weeks of the study. The treatment policy estimand results show that between baseline and week 68, the estimated mean body weight change was -17.4% among the participants who continued with semaglutide and -5.0% among those who switched to placebo (difference, -12.4 percentage points (95% CIs -13.7 to -11.0)). Results based on the trial product estimand were similar. Based on Figure 2 in Rubino et al.,[2] and considering that it is proposed that patients would receive two years treatment with semaglutide rather than 20 weeks, the ERG consider that the company's assumption of weight regain within three years is reasonable.

3.2. NHSE comment on relevance of QRISK 3 equations

The NHSE comment that they disagree with the use of the QRisk-3 equations to predict cardiovascular events in the economic model and view the use of this analysis as inappropriate. They note that semaglutide would be given for a maximum two-year period when weight regain will then inevitable and there will be a loss of effect on the surrogate cardiovascular (CV) risk factors.

The ERG notes that this point concerning the appropriateness of the risk equations is discussed in the ACD section 3.15. We agree with the discussion in this section, namely that there are several limitations to these risk equations but there may be no better practical alternative.

3.3. NHSE comment on lack of evidence on longer-term cardiovascular outcome benefits

NHSE comments that there is a lack of evidence to support an assumption of longer-term beneficial CV outcomes for a time-limited use of the semaglutide (i.e. use of the drug for up to a maximum of two years). They state that even if semaglutide were to be continued and patients continue to respond, current evidence suggests that no benefit on CV outcomes can be assumed, at least up to 7 years with maintenance of weight loss. NHSE cite recently published, real-world data from the CPRD-GOLD database cohorts that found that improvements in surrogate risk factors for CV disease associated with intentional weight loss were not associated with any benefit in any of the CV outcomes of atrial fibrillation, heart failure, unstable angina or myocardial infarction. NHSE state that if it is assumed that there is no CV benefit in the economic model, this markedly increases the ICER with time-limited (maximum two years) use of semaglutide.

The ERG notes that any differences in CV event outcomes between treatments over time are likely to be small, as a small number of events are likely to be observed. Benefits on CV outcomes may not be detectable even in large, real-world studies, especially if they have limited follow-up periods. Further we note that the study by Haase et al[3] suggests that there are considerable risk reductions associated with a lower BMI for type 2 diabetes (41%), sleep apnoea (40%) and other complications. We provide scenarios using the company's model (with the ERG's preferred assumptions) to exclude complications due to acute coronary syndrome and stroke from the model to thus show the effect of excluding benefits for CVD (Table 1). Excluding the long-term benefits on CVD has only a small impact on the model results.

Table 1 ERG base case with different assumptions for long term benefits

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case	Diet & physical activity	[redacted]	[redacted]	£16,337
	Semaglutide 2.4mg		[redacted]	
Exclude CVD benefits	Diet & physical activity	[redacted]	[redacted]	£18,376
	Semaglutide 2.4mg	[redacted]	[redacted]	
Exclude CVD and diabetes benefits	Diet & physical activity	[redacted]	[redacted]	£26,668
	Semaglutide 2.4mg	[redacted]	[redacted]	
Exclude benefits for CVD, diabetes, knee replacement and sleep apnoea	Diet & physical activity	[redacted]	[redacted]	£34,044
	Semaglutide 2.4mg	[redacted]	[redacted]	

4. References

1. Le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389(10077):1399-409. doi: 10.1016/s0140-6736(17)30069-7 [published Online First: 2017/02/27]
2. Rubino D, Abrahamsson N, Davies M, et al. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. *JAMA* 2021;325(14):1414-25. doi: 10.1001/jama.2021.3224
3. Haase CL, Lopes S, Olsen AH, et al. Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database. *Int J Obes (Lond)* 2021;45(6):1249-58. doi: 10.1038/s41366-021-00788-4 [published Online First: 2021/03/05]

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Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Semaglutide for managing overweight and obesity

Additional scenarios requested by NICE

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Date completed	10 March 2022

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1. On 9th March, NICE requested the following additional analyses using the ERG base case:

- ERG base case + removal of CVD benefits + weight rebound within 2 years
- ERG base case + removal of CVD benefits + weight rebound within 2 years + 3 year treatment

The ERG completed these analyses and the results are shown in Table 1. With CVD benefits excluded, weight loss assumed to be regained within 2 years and a 3 year treatment duration for semaglutide 2.4 mg, the ICER increases from £16,337 per QALY to £23,582 per QALY.

Table 1 ERG base case with different assumptions for long term benefits

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
ERG base-case	Diet & physical activity	[redacted]	[redacted]	£16,337
	Semaglutide 2.4mg			
Exclude CVD benefits	Diet & physical activity	[redacted]	[redacted]	£18,376
	Semaglutide 2.4mg			
Exclude CVD benefits + weight rebound within 2 years	Diet & physical activity	[redacted]	[redacted]	£23,718
	Semaglutide 2.4mg			
Exclude CVD benefits + weight rebound within 2 years + 3 year treatment	Diet & physical activity	[redacted]	[redacted]	£23,582
	Semaglutide 2.4mg			