Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Most comments have been responded to individually. Some comments have been grouped into 7 themes. Responses to these themes can be found tabulated at the end of this document.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
ABPI	General	1.8 Equality and other considerations	General	General	The stakeholder workshop report highlights that "The importance of considering productivity impacts and access for children and adolescents was highlighted," however there is no discussion of productivity inputs in the reference case extension or in the remaining supporting documents and productivity costs are not considered as part of the reference case extension. The government has clearly stated its intent to drive UK economic growth and recognises the significant role the Life Sciences sector plays in this. The NHS 10 year plan states that a key goal is to "*unlock broader economic benefits for the UK, helping to get people back into work.*" The plan also states that "*poor health is increasingly a major barrier to people finding work. Health related economic inactivity has increased by 700,000 people since 2020. This government will support people into good work to support their health, and we will also ensure good population health, to support the labour market, deliver economic growth and prosperity.*" Collaborations involving collecting data on changes in employment status in the context of the obesity space are highlighted, for example "*a world-first 'real world evidence' study*	Thank you for your comment. This reference case extension cannot contradict NICE's methods manual, which currently only allow the inclusion of productivity gains for interventions carried out from a workforce perspective.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					evaluating the effectiveness of weight loss medication, including gathering data on health-related quality of life and changes in participants' employment status." The potential benefits of weight-loss products on productivity are not captured within the reference case extension. The ABPI considers that, at the very least, scenario analyses with a wider perspective, which capture impacts on productivity, should be considered by committees.	
ABPI	Questions	Question 1	Question 1	Question 1	*"1. How can NICE support stakeholders to ensure this reference case extension is implementable within the usual timelines of each of NICE's guidance programmes (that is Medicines Evaluation, HealthTech, and Guidelines)?"* Implementation of any reference case extension would be supported by timely, clear communication to relevant stakeholders on the details of the extension (if already existing) or the timelines for its development.	Thank you for your comment. We agree that timely and clear communication to stakeholders is important.
ABPI	Questions	Question 2	Question 2	Question 2	*"2. Is the distinction between 'required' and 'recommended' helpful in bridging the gap between enhancing consistency and allowing flexibility?* The ABPI considers that this distinction is useful. However, we note that the term 'recommended' encompasses a wide range of uncertainty levels, and there is a risk that committees may	Thank you for your comment.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					over-prioritise 'recommended' approaches with high uncertainty, even when more robust alternatives are presented by either the company or the EAG. Based on previous company experience, non-reference case analyses are infrequently accepted by committees. While it is understood that companies can justify providing alternative analyses, it is important that, in practice, these justifications are given due consideration and that committees are seen to accept non-reference-case approaches where appropriate. The position statement on disease-specific reference models states that "*Deviations from reference case extensions should be explained and justified by companies, EAGs and guideline developers, and agreed through committees and NICE's quality assurance processes. NICE will keep the reference case extensions under review to assess whether updates are needed.*" Further clarity on the processes for agreeing deviations would be beneficial to stakeholders. We note that deviations should be allowed at any point of the appraisal process (not just at the scoping stage), that further clarity on the mechanism for agreement on deviations and	We do not think that the 'more robust' approaches will be overlooked by EAGs and committees. Each guidance producing directorate will develop processes for implementing reference case extensions. Potential deviations need to be discussed and evidenced at the point in the process at which they are proposed, for example at scoping, within submissions or in response to draft guidance consultation. We do expect justification for deviations from both required and recommended statements, but deviations to required statements would only be accepted in exceptional circumstances.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					who is involved in this would be valuable, and that it should be clear whether agreement is needed for both "required" and "recommended" elements or simply for "required" elements.	
ABPI	Questions	1.2 Intervention and comparators	Question 4	Question 4	"4. *Is it helpful to specify appropriate comparators or will this present operational challenges in applying the reference case extension? (see 1.2.2-1.2.6)?"* The specification of comparators is more appropriate to conduct as part of the individual scope for each appraisal. Specification of comparators within the reference case extension may present operational challenges for NICE, as it will require the reference case extension to be constantly monitored and updated to ensure that the specification of comparators remains relevant.	Thank you for your comment. There were several stakeholders who responded in support of providing the minimum comparators relevant for each intervention category as per the reference case extension. These comparators are sufficiently top level that they are unlikely to become outdated, therefore it was decided to keep them in the reference case extension.
ABPI	Questions	1.8 Equality and other considerations	Question 6	Question 6	*"6. The role of distributional cost-effectiveness analysis (DCEA) is referred to in the NICE manuals but is not currently included within the NICE reference case. Do you think there is a role for DCEA to inform decision-making specifically around the management of obesity (see 1.8.1)?"* The methods currently recommended in the NICE manual to analyse health inequalities are	Thank you for your comment. The statement that followed the one on DCEA clarified when qualitative considerations should be made beyond the results of the cost-utility analysis.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					likely to be appropriate for obesity, provided qualitative evidence is acceptable when a DCEA is not feasible. Further recommendations in the reference case extension on preferred data sources for DCEA may be valuable, but should be provided at the 'recommended' level to ensure sufficient flexibility if other appropriate data sources are identified.	
Amgen (Europe) GmbH	Obesity RCE report	1.1 Population	002 003 004 007 008	003 – 019 014 – 015 001 – 005 003 – 026 001 – 024	**<u>Consideration of all relevant ORCs</u>** Sections 1.1.1, 1.1.5, 1.1.6, and 1.3.6 – 1.3.11 identify T2DM and ASCVD as required ORCs for inclusion in all cost-effectiveness models. Other important ORCs, such as atrial fibrillation, cancer, chronic heart failure (CHF), chronic kidney disease (CKD), dyslipidaemia, hypertension, mental health conditions, MASH/MASLD, osteoarthritis (OA), and obstructive sleep apnoea (OSA), are classified as optional and only recommended for sensitivity analysis or inclusion when direct evidence exists. Given the established burden and clinical relevance of these conditions in people living with overweight or obesity, restricting them to optional inclusion is likely to lead to divergent modelling approaches across manufacturers and limit comparability of submissions. To avoid structural heterogeneity, the reference case should promote a disease-natural-history perspective. rather than a clinical evidence-	Thank you for your comment. The list of health states is a summary of those that have been modelled and are supported by evidence. They do not include every outcome that could be modelled. We have clarified the criteria for selecting outcomes, which include evidence of an association between weight loss and improved outcomes, hence there need not necessarily be direct evidence from a randomised trial. We have broadened the number of included ORCs used as suggested outcomes in the model: • Hip replacement in addition to knee replacement to cover osteoarthritis, which otherwise is mainly treated by low-cost medicines • Chronic kidney disease • Mental health care costs have been added.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					driven perspective. The NICE Methods Guide[1] states that CEMs should be informed by knowledge of the natural history of the disease (Section 4.6.18) and that structural assumptions must be explored and justified (Section 4.6.3). This supports modelling obesity in a way that captures its multisystem consequences, even when some treatment effects rely on indirect evidence, risk equations, or justified assumptions. Such an approach keeps the structure aligned with the disease's natural history while transparently managing uncertainty. One solution would be for NICE to provide a reference model blueprint, or a full executable reference model, incorporating all major ORCs. Manufacturers could then tailor or justify deviations, reducing both analytic burden and variability across submissions. The requirement for direct evidence for each ORC may also delay access across relevant subpopulations, as it implicitly necessitates clinical trials evidence covering every condition of interest. GLP-1 receptor agonists already demonstrate or are evaluating effects across multiple ORCs (including CHF, CKD, OA, and OSA) in phase 3 programmes, but not all treatments have dedicated obesity trials for every outcome. A class-effect assumption for the *direction* of effect, consistent with precedent in earlier obesity appraisals, could provide a pragmatic approach until more definitive	We now specify to subgroup by type or number of obesity-related comorbidities; the conditions listed are examples and does not preclude subgrouping by other comorbidities if they can be demonstrated as being clinically or economically important.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					evidence becomes available but further guidance is necessary within the reference case. *[1] National Institute for Health and Care Excellence (NICE) (2022). NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36*	
Amgen (Europe) GmbH	Obesity RCE report	1.1 Population	004	003 – 005	**Regression analysis** Section 1.1.6 recommends conducting regression analysis by BMI/BMI category and type and number of comorbidities. It is unclear which data sources should be used for these analyses, and whether they are intended to generate inputs for the model or to provide supportive evidence alongside the cost-effectiveness analysis. We request that NICE clarify both the intended purpose of these regressions, as well as the preferred specification and data sources to be used, to ensure consistency across submissions.	Thank you for this comment. We have deleted the statement as it was unclear. The section on clinical parameters now contains more information about estimating treatment effects.
Amgen (Europe) GmbH	Obesity RCE report	1.2 Intervention and comparators	004	010 – 014 018 – 021	**Comparators** Sections 1.2.1 and 1.2.3 state for new medicines targeting overweight and obesity, the model should include relevant medicines that are established practice in the NHS for managing weight and ORCs. However, for subpopulations with specific ORCs at baseline, it remains unclear whether relevant comparators should be chosen based on the broader weight-management indication or based on the availability of direct evidence in the ORC-	Thank you for your comment. Obesity related comorbidity (ORC) treatments should be included as background treatments in both arms rather than as comparators (see 1.2.10). The interventions of interest in this reference case extension are ones that reduce weight. The two statements have been edited to clarify this.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					specific treatment pathway. From a natural-history perspective, baseline ORCs are integral to the progression of obesity and influence both treatment options and outcomes. Without clearer guidance, manufacturers may adopt different interpretations of how to align comparator selection with the disease's natural history, potentially leading to inconsistent or non-comparable submissions. This is particularly important for analysis in subpopulations with baseline ORCs. Clearer guidance on how comparators should be defined for subpopulations with baseline ORCs would support consistency and transparency across submissions.	
Amgen (Europe) GmbH	Obesity RCE report	1.3 Model structure and health states	006	008 – 015 & 019 – 023	**Model structure** The draft reference case states that any modelling approach may be used if it can be clearly interrogated, validated, and can capture all relevant differences in costs and outcomes (Section 1.3.1). However, the detailed recommendations are largely framed around fixed-cycle cohort models (Sections 1.3.1, 1.3.2, 1.3.4, 1.3.5, 1.4.6). As a result, the reference case provides limited direction for continuous-time approaches. such as discrete event simulation (DES), despite these approaches offering a more natural representation of the disease process in obesity.	Thank you for your comment. We agree that discrete event simulation is suitable for modelling and has some advantages. However, many stakeholders are more familiar with state transition models, and these are the most typical model in the area. We retain a preference for state transition models and therefore the language throughout the document relates to them. Model developers who build discrete event simulations will understand how to replicate the conditions of a state transition model. With regard to handling comorbidity interactions, we have described this throughout the document, including for baseline risks,

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					A continuous-time framework is particularly well aligned with several requirements in the reference case, including modelling the duration of living with overweight or obesity and its effect on future outcomes (Section 1.4.9), incorporating obesity-related comorbidities (ORCs) through event-driven health state transitions (Section 1.3.10), avoiding double-counting of mortality (Section 1.5.8), and mitigating risk overestimation in cycle-based structures (Section 1.4.6). However, it is unclear how guidance written focusing on fixed-cycle models should be interpreted for continuous-time hazard models. More explicit guidance is needed to ensure consistent assessment of submissions, whether using fixed-cycle length or continuous time-based model structures, including: 1. expectations for transparency and validation in continuous-time frameworks 2. acceptable approaches for modelling competing risks and comorbidity interactions how cycle-based requirements in the reference case should translate to models without fixed cycles.	subgrouping, treatment effects, costs and utilities.
Amgen (Europe) GmbH	Obesity RCE report	1.3 Model structure and	007 008	003 – 014 & 021 – 026	**<u>Granularity of T2DM and ASCVD modelling</u>** Sections 1.3.6, 1.3.8, and 1.3.9 of the draft reference case specify required health states for	Thank you for your comment. Where obesity medications such as incretin agonists have been recommended by NICE, it has invariably been for people with obesity and at least one other

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		health states		001 – 006	modelling type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) in cost-effectiveness models for overweight and obesity. However, the disease pathways described are substantially less detailed than those typically used in standalone T2DM or ASCVD appraisals. Past NICE submissions in obesity have implemented simplified versions of these pathways, and without clearer guidance, manufacturers may differ in how much complexity they include. This risks non-comparability across submissions and inconsistent interpretation by Evidence Review Groups. More explicit guidance is needed on the expected structure for T2DM and ASCVD disease progression, including treatment escalation pathways, transition logic, and clinical event definitions. In particular, the rationale for mandating inclusion of a T2DM population requires clarification. Most anti-obesity medicines (e.g., GLP-1 and GLP-1/GIP agonists) are also indicated for T2DM and deliver clinically important benefits beyond weight loss, especially glycated haemoglobin (HbA1c) improvements, which drive treatment progression and future complications. Comprehensive T2DM models must capture these dynamics and the full spectrum of T2DM-related comorbidities, but such complexity cannot be reliably represented within an obesity	comorbidity, including T2DM. Therefore, there is little logic in in a framework for obesity, which excludes any risk factors. However, in recognition that there is great heterogeneity in risk and in treatment pathways, we have defined strata that should not be combined. This includes separating out people withT2DM and ASCVD. We have described the minimal number of outcomes and events to be modelled where there is direct evidence of a treatment effect and where there is not. We do not mandate the inclusion of a T2DM population in any guidance. We do not expect every piece of guidance to cover all 8 strata. We say that if you are including these people then they should be modelled separately. We agree that for people with a specific comorbidity at baseline (and obesity or overweight), for example T2DM or ASCVD or MASH then we expect good practice in modelling these comorbidities to be followed while maintain consistency with the overweight and obesity management reference case extension. A MASH reference case extension is in development, which will add more detail for people with weight-related liver disease.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					model, leading to underestimation of benefits for people with T2DM. This was also the presented rationale on why the recent tirzepatide appraisal (TA1026) did not include individuals with T2DM in the base case. If the intention is to ensure appropriate ORC coverage, further clarification from NICE would be helpful on whether ORCs that have already been appraised and recommended in earlier GLP-1 evaluations may be considered for simplified modelling or exclusion, where justified.	
Amgen (Europe) GmbH	Obesity RCE report	1.3 Model structure and health states	008 011	002 – 006 019 – 023	**Remission** Section 1.3.9 states that remission of T2DM (unless directly evidenced) and ASCVD should not be modelled. However, Section 1.5.2 indicates that treatment discontinuation due to remission should be incorporated into the model. These statements introduce uncertainty regarding how remission should be interpreted and modelled. Additional clarity would be helpful on: - the ORCs for which remission is considered relevant and associated definition of remission (e.g., the magnitude and duration of improvement required to qualify as remission) - how relapse should be modelled. Further guidance is also needed on whether remission should necessarily lead to full treatment discontinuation, or whether a	Thank you for your comment. In the section on discontinuation, we have changed the wording from 'remission' to 'achievement of healthy weight' for clarity. It would be beyond the scope of this reference case extension to describe in detail stopping rules for all treatments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					reduction in treatment dose or dosing frequency would be more appropriate as a form of maintenance therapy to help prevent relapse. Given that weight regain and subsequent deterioration are common after stopping treatments, a discontinuation rule based solely on remission may not reflect optimal long-term management. Clear direction on how NICE expects these pathways to be represented would help ensure consistent and clinically plausible modelling across submissions. Further guidance would also be beneficial to clarify how discontinuation due to inefficacy should be applied across patient groups. The draft reference case appears to focus on weight-based criteria, but it is unclear whether the same discontinuation rule should apply to individuals treated primarily for weight loss and those with specific ORCs at baseline. For some subpopulations, the clinically relevant measure of treatment benefit may relate more directly to ORC progression rather than a prespecified weight-loss threshold. Clarification on whether discontinuation rules should be uniform across all patients or tailored to reflect the primary therapeutic objective in subpopulations with ORCs would help ensure consistent, clinically appropriate modelling across submissions.	
Amgen (Europe) GmbH	Obesity RCE report	1.4 Clinical paramete	010	001 – 006 &	**Risk equations**	Thank you for your comment. This point is covered within our thematic response to related comments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		rs and variables (treatment effects and risk prediction)		009 – 012	While the draft reference case highlights the need for risk equations to be appropriately justified and validated (Sections 1.4.4 and 1.4.5), it does not provide guidance on which data sources are considered most suitable or how the appropriateness of those sources should be assessed. In the absence of such direction, manufacturers may reasonably select different datasets or risk equations, which could lead to heterogeneity in long-term predictions and reduced comparability across submissions. Providing clearer expectations, such as criteria for acceptable data sources, examples of preferred or benchmark datasets, or guidance on when newer external evidence should supersede older studies, would help promote consistency. It may also be beneficial for NICE to maintain an updated list of preferred sources, particularly as more contemporary datasets become available, reducing continued reliance on older evidence bases, such as the UK Prospective Diabetes Study (UKPDS) 82. In addition, the draft guidance specifies that predicted outcomes from risk equations should be calibrated using trial data or real-world evidence, but it does not outline recommended methodological approaches for calibration or how such calibration should be implemented in practice. Clarification on acceptable calibration methods, validation procedures, and the	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					preferred sources for conducting calibration and validation (as well as the level of documentation expected) would further support consistent and transparent modelling across submissions.	
Amgen (Europe) GmbH	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	013	001 – 005 010 – 014	**Mortality** Section 1.5.8 requires the model to incorporate either BMI-adjusted mortality multipliers or condition-specific mortality multipliers, but not both, to avoid double counting. We recognise this risk of double counting. However, applying only one set of multipliers may be overly conservative and may underrepresent the full mortality burden experienced by people with obesity and ORCs. Of note, Bhaskaran et al. (2018), which has been used to adjust all-cause mortality in previous NICE obesity appraisals, reported age- and sex-specific associations between BMI and all-cause mortality in a large UK cohort. However, the overall association between BMI and mortality was driven by varying associations with individual case-specific mortality outcomes. Therefore, relying on a single set of multipliers does not account for this variation and might lead to misrepresentation of the overall disease burden. the proposed reference case for mortality may lead to an underestimation of overall mortality, and a combined approach could be appropriate. Clear guidance on how BMI-specific and condition-specific mortality multipliers can be	Thank you for your comment. Please refer to the thematic response "mortality".

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					integrated in a way that minimises the risk of double counting, while still allowing models to reflect the full mortality benefits of new treatments. Furthermore, there is no guidance on how competing mortality risks should be handled across different modelling approaches, particularly in cohort state-transition models, where competing-risk challenges are more pronounced than in discrete-event patient-level simulations. Additional guidance on acceptable adjustments would help to support consistent and transparent modelling approaches across submissions.	
Amgen (Europe) GmbH	Obesity RCE report	1.6 Measuring and valuing health effects	014	003 – 007	**Utilities** Section 1.6.2 states the best source for utility would be a single dataset that controls for weight, comorbidity and other variables such as age and sex. However, such comprehensive datasets remain rare in practice. While some studies have modelled utility as a function of BMI, comorbidities, and demographics using individual datasets (e.g., Health Survey for England [Luah et al., 2024][2]), these sources typically do not contain the full spectrum of ORCs or the full range of clinically relevant covariates required to meet the specification outlined in Section 1.6.2. Clinical trial datasets similarly do not include all relevant ORCs, nor adequately represent all subpopulations needed	Thank you for your feedback. In the rationale for this section, we highlight a potential single dataset, an analysis by Luah et al. (2024), which is a regression analysis of Health Survey for England data, which estimated the association between BMI and EQ-5D-5L among the general population in England. The analysis also controlled for comorbidities such as diabetes, heart and circulatory disease, respiratory disease, musculoskeletal disease, cancer and mental health disorders. The HSE data is publicly available and could be re-analysed for provide health state utility values for an obesity model.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					for comprehensive utility estimation. Consequently, it is often necessary to combine information from multiple high-quality sources or published regression functions rather than rely on a single unified dataset. Clarification on acceptable approaches when such a comprehensive single source is unavailable would help promote consistency across submissions and reduce the risk of divergent utility assumptions. [2] *Luah XW, Holst-Hansen T, Lübker C. The association between body mass index and health-related quality of life in the 2017 and 2018 health survey of England data: A cross-sectional observational analysis. Diabetes Obes Metab. 2024;26(6):2318-2328. doi:10.1111/dom.15546*	
AstraZeneca	Obesity RCE report	General	General	General	AstraZeneca thanks NICE for prioritising consistent, evidence-based modelling for overweight and obesity. AstraZeneca remains committed to improving care across cardiovascular, renal and metabolic conditions, and welcomes the opportunity to comment on the draft obesity reference case extension with a shared goal of enhancing model consistency across guidance. AstraZeneca supports many of the recommendations in the extension, particularly those that strengthen consistency in model structure, inputs, assumptions, comparators and	Thank you for your comments. We have provided detailed responses throughout the document to your individual points.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					reporting across evaluations. However, there are areas which represent significant missed opportunities to further improve the quality and consistency of economic modelling for people with overweight and obesity. The main areas of concern include: • Required stratification at the specified granularity (1.1.1) risks indirect treatment comparisons being infeasible and may lead to underpowered subgroup estimates. AstraZeneca proposes changing to "recommended" and permitting aggregation where justified, for example, when strata specific data needed for indirect comparisons are unavailable • Additional subgrouping by age and sex as well as body-mass index (BMI) category and comorbidity in cohort models (1.3.5) should be performed only when comparative data are available • Capturing chronic kidney disease (CKD) status and presence of chronic heart failure (HF) in model health states should extend beyond strata containing people with either type 2 diabetes mellitus (T2DM) or	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					atherosclerotic cardiovascular disease (ASCVD). AstraZeneca suggests amending recommendation 1.3.7 to reflect presence of evidence of a treatment effect rather than limiting inclusion of strata based on T2DM or ASCVD status. AstraZeneca would particularly like to highlight concerns relating to multiple sections within the obesity reference case requiring or recommending particular subgroup analyses. When taken in combination, these compound to create a very large number of required analyses, many of which may not be informative for decision-making given technical challenges relating to limited trial sample sizes and lack of publicly available data for key comparators in established NHS practice. By making such analyses a rigid component of the reference case in spite of such inevitable technical challenges, it risks causing undue complexity and burden in the appraisal process for weight management therapies, and is likely to delay and fragment access for patients. AstraZeneca acknowledge that NICE may seek to explore certain subgroups to understand and mitigate specific uncertainties, but suggest that this would be better achieved by requests on a case-by-case basis, where data permits.	

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
AstraZeneca	Obesity RCE report	1.1 Population	002	003 – 019	**Concern** Requiring stratification at the level of granularity specified in recommendation 1.1.1 may lead to indirect treatment comparisons being infeasible given the current limitations in publicly available data for key comparators. In addition, it risks the cost-effectiveness model relying on subgroup estimates for efficacy, which may be statistically underpowered. **Rationale** The necessary subgroup-level data may not be publicly available for key comparators, including medicines established in NHS clinical practice, which may prevent the feasibility of conducting methodologically sound indirect treatment comparisons (ITC) within specific strata. For example, if a new treatment were compared with tirzepatide in the population recommended in TA1076[1] (people with a BMI of at least 35 kg/m² and at least one weight-related comorbidity), there is currently no publicly available evidence to enable stratified comparisons by ASCVD status. Consequently, indirect comparisons within exclusively ASCVD or no-ASCVD strata cannot be constructed. Similar limitations are likely for other strata where the relevant comparator is an NHS medicine. Additionally, clinical trials in obesity are not typically powered to detect treatment differences	Thank you for your comment. Please see our themed response on Population: number of subgroups.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					between populations with obesity and overweight or with and without atherosclerotic cardiovascular disease (ASCVD). This limits the robustness and interpretability of estimates within the specified strata. Furthermore, the additional subgroup requirements outlined in Recommendations 1.1.2–1.1.5, would further fragment sample sizes and increase uncertainty, compounding issues of low power, unstable estimates, and reduced comparability across evidence sources. For example, in a single stratum containing people with obesity and T2DM or ASCVD, the sensitivity analyses could require dividing the population in up to 7 different subgroups (three different BMI categories; with/without CKD and with/without HF) **Summary** AstraZeneca proposes revising the recommendation from "required" to "recommended," and permitting aggregation when appropriately justified, for example the absence of published strata-specific data precluding a sufficiently robust ITC.	
AstraZeneca	Obesity RCE report	1.2 Intervention and comparators	005	001 – 009	**Concern** While AstraZeneca agrees with recommendation 1.2.4, requiring that new bariatric procedures are compared with bariatric procedures already established in NHS clinical practice, bariatric procedures are not a relevant comparator for	Thank you for your comment. This is a recommended statement rather than a required statement and applies to the specific populations listed in the sub-bullets to reflect the NICE obesity clinical guideline. If modellers do not include bariatric procedures as a comparator to medicines for these populations, a clear

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					weight management therapies and so it should be made clear that recommendation 1.2.6 only applies for appraisals of new bariatric procedures. **Rationale** The NICE scope and appraisals for tirzepatide [TA1026][1] and semaglutide [TA875][2] did not include bariatric procedures as a relevant comparator due to the fact that it is only available for a small minority of people. In these appraisals, bariatric surgery was instead included as a one off-event that a proportion of patients may receive in practice, while patients continue to receive their weight management therapy. Bariatric surgery is only recommended in the NICE guideline [NG246] on 'Overweight and Obesity Management' only for a restricted cohort of patients, and the procedure is rarely used in clinical practice with around 0.2 % of eligible patients actually receiving this treatment.[3] The NHS England National Obesity Audit (NOA) reported that only 5479 people received bariatric surgery between 2023–24.[4] As such, bariatric surgery is not a relevant comparator for weight management therapies. **Summary** AstraZeneca proposes that 1.2.4 and 1.2.6 are updated to:	justification would be required and explanation added that it has been included later in the pathway.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					1.2.4 As a minimum, new bariatric procedures should also be compared with (required) bariatric procedures established in NHS clinical practice, such as gastric bypass surgery (except where contraindicated) • Assessment for bariatric procedures (with procedure type clearly defined and justified) could be comparators in these relevant subgroups: (recommended) ○ adults with a body mass index (BMI) of 30 kg/m² or more who have recent onset type 2 diabetes mellitus (T2DM), or ○ adults with a BMI between 35 kg/m² and 39.9 kg/m² with a significant health condition that could be improved if they lost weight, or ○ adults with a BMI of 40 kg/m² or more.	
AstraZeneca	Obesity RCE report	1.3 Model structure and health states	007	003 – 014	**Concern** Recommendation 1.3.6 could be interpreted as health states needing to be specific to each weight category, however in previous appraisals (TA1026 [Tirzepatide for managing overweight and obesity] and TA875 [Semaglutide for managing overweight and obesity])[1, 2] weight change over time has been captured continuously without the need for specific health states for each weight category. Capturing weight exclusively by health states, and not by	Thank you for your comment. The health states were intended to be a minimum specification. We have revised the requirement as you have suggested.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					the weight trajectory over time, may represent a less accurate approach compared to the approach taken in these prior appraisals, as it is less sensitive to small changes in BMI (i.e. change may only be captured when patients move from one weight category to another). Moreover, capturing granular changes in BMI would improve modelling accuracy because BMI is typically an input to key risk equations often used in obesity modelling (including QDiabetes, QR4, QRisk3)[5-7], and there is a well-established relationship between BMI and utility.[8] **Summary** AstraZeneca proposes amending the recommendation wording to make it clear that weight and BMI can be captured without the need for specific health states. AstraZeneca proposes amending recommendation 1.3.6 to: For strata containing people without type 2 diabetes mellitus (T2DM) or atherosclerotic cardiovascular disease (ASCVD) at baseline, the health states included in the model should capture all of the following: (required) • T2DM status: 'no T2DM' or 'prediabetes' or 'T2DM'	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					• ASCVD status: 'no ASCVD' or 'post-myocardial infarction (MI)' or 'post-stroke' or 'post-stroke and MI' • ASCVD acute events: 'MI' or 'stroke' or 'stroke after MI' or 'MI after stroke' • weight category: captured either as distinct health states ('healthy weight' or 'overweight' or 'obesity'), or via weight/BMI trajectory without requiring specific health states • line of treatment (if applicable) 'alive' or 'dead'.	
AstraZeneca	Obesity RCE report	1.3 Model structure and health states	007	015 – 020	**Concern** Recommendation 1.3.7 limits the capturing of CKD status and presence of HF to strata containing people with T2DM or ASCVD, however it is possible that other strata could contain populations with CKD and HF. Capturing of CKD status and presence of HF should be determined by presence of evidence of a treatment effect in these comorbidities rather than population strata. **Rationale** AstraZeneca recognises that prevalence of CKD and HF is higher across T2DM and ASCVD populations, however these comorbidities may also be present in people with overweight or obesity without either T2DM or ASCVD. In addition, it is plausible that treatments for people with overweight or obesity may show benefits in	Thank you for your comment. We initially restricted CKD status to cohorts with T2DM or ASCVD, on the basis that some existing models did not include CKD and the incidence of CKD is likely to be lower. However, for clarity, we have recommended that CKD/CHF be included for all strata.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					CKD and HF in populations without T2DM or ASCVD. Epidemiological evidence indicates that overweight and obesity are associated with higher incidence of CKD and HF across increasing BMI categories.[9, 10] Moreover, evidence from weight-loss pharmacotherapy suggests improvements in HF-related outcomes in populations without T2DM.[11, 12] Conversely, if there is no evidence of a treatment effect, including CKD and HF health states might represent an unnecessary complexity being added to the model. **Summary** AstraZeneca suggests the recommendation should be extended to all strata provided there is direct evidence of a treatment effect. AstraZeneca proposes amending recommendation 1.3.7 to: In strata which there is evidence of a treatment effect, the health states should capture: (recommended) • CKD status (No CKD vs Stages 1-4 vs Stage 5) • presence / absence of chronic heart failure	
AstraZeneca	Obesity RCE report	1.4 Clinical parameters and variables	009	011 – 019	**Concern** AstraZeneca agrees that the surrogates included in recommendation 1.4.3 are relevant for predicting change in the incidence of ASCVD	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		(treatment effects and risk prediction)			and T2DM. However, in situations where there is no clinical trial directly comparing the intervention with the chosen comparator, comparative data on the listed surrogates may not be available, for example, if the chosen comparator is an NHS medicine, but the available clinical trial evidence compares against behavioural intervention alone. **Summary** AstraZeneca suggests amending recommendation 1.4.3 to: The following surrogate outcome measures should be included as a minimum for predicting change in the incidence of ASCVD and T2DM when comparative data is available: (recommended) • Weight and body mass index (BMI) • Systolic blood pressure • HbA1c • Cholesterol (HDL and LDL) • estimated glomerular filtration rate (eGFR)	
AstraZeneca	Obesity RCE report	1.3 Model structure and health states	006 – 007	024 – 026; 001 – 002	**Concern** The further subgrouping of population by age, sex, BMI category and comorbidity recommended in 1.3.5 in addition to the strata specified in recommendation 1.1.1 may result in increased uncertainty due limited statistical powering in clinical trials. In addition, subgroup	Thank you for your comment. In the case of relative treatment effects, you can test for heterogeneity between subgroups. If there is no statistical evidence of a difference, then the overall treatment effect can be used for each subgroup. If there is evidence of

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					specific data for comparator treatments may not be available in published literature to allow for a methodologically sound comparison to the intervention. **Rationale** Similar to recommendation 1.1.1, clinical trials in obesity are not typically powered to detect treatment differences between subgroups of different age, sex, BMI category and comorbidity. This limits the robustness of estimates within the specified subgroups and will likely increase uncertainty in the model. For example, in a single stratum containing people with obesity there could be more than 24 different subgroup estimates required, assuming no evidence of linearity of treatment effects (2x sex; 2x age; 2x comorbidity; 3x BMI category). In addition, the necessary subgroup-level data may not be publicly available for key comparators, including medicines established in NHS clinical practice which may undermine the feasibility of conducting indirect treatment comparisons to specific subgroups. However, AstraZeneca recognises the value of assessing the variability in results that can occur when taking the subgrouping approach, particularly when there is no evidence of linearity of effects, as this may represent a more accurate estimate of expected clinical efficacy. Therefore, AstraZeneca believes a subgrouping	heterogeneity, then you should not be using overall pooled effects in the model. If the study is under-powered to detect subgroup differences, then the overall pooled estimate will be used, which is no worse than not doing a subgroup analysis at all. Even where treatment effects are the same across different subgroups, there still would be value in subgroup analyses if baseline risks vary between subgroups, which they frequently do.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					approach should be carried out when there is sufficient data to allow for a comparison to the appropriate comparator (for example head-to-head trial data, or ITC data specific to the subgroup is available). **<u>Summary</u>** AstraZeneca proposes amending the recommendation to specify that subgrouping should be carried out in sensitivity analysis only when appropriate data for the subgroup is available for a feasible comparison or limiting the comparison to behavioural interventions alone. AstraZeneca proposes amending recommendation 1.3.5 to: If a cohort approach is <u>taken and sufficient comparative data is available,</u> then subgrouping by age and sex as well as BMI category and comorbidity is advised (unless there is evidence of linearity of effects) with weighted-average costs and QALYs calculated" (recommended)	
AstraZeneca	Questions	Question 1	Question 1	Question 1	AstraZeneca thanks NICE for its commitment to timely and consistent implementation across programmes and would encourage NICE to consider the following approaches: • Implementing a standardised checklist covering the key aspects of the obesity reference case, used to document and justify modelling decisions, data sources, assumptions, and any	Thank you for your comment. We will consider developing a checklist as part of our ongoing implementation activities. Each of NICE's guidance producing programmes are developing processes to facilitate the use of reference case extensions.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					proposed deviations to the recommendations • Establishing a clear process, or incorporating into an existing process (i.e. as part of the decision-problem meeting), for pre submission discussions between the committee and the company to review and agree any potential deviations from the reference case, with rationale and supporting evidence recorded.	
AstraZeneca	Questions	Question 2	Question 2	Question 2	AstraZeneca agrees the distinction between "required" and "recommended" is helpful because it provides clear minimum expectations to enhance consistency while preserving flexibility to reflect evidence availability and feasibility across interventions and populations. To further improve clarity on recommendations we suggest NICE clarifies if and when deviations from "required" recommendations are permissible, for example, where unavoidable due to the lack of comparative data to a specific strata. As mentioned in the answer to Question 1, AstraZeneca suggests establishing a clear process for pre submission discussions between the committee and the company to review and agree any potential deviations from the reference case, with rationale and supporting evidence recorded.	Thank you for your comment. Each guidance producing directorate will develop processes for implementing reference case extensions. We acknowledge that early engagement would be helpful. Lack of data for a comparator in a specific stratum might be considered an adequate justification for deviation. But NICE would expect that all reasonable actions have been taken to obtain that data. Potential deviations need to be discussed and evidenced at the point in the process at which they are proposed, for example at scoping, within submissions or in response to draft guidance consultation.

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
AstraZeneca	Questions	Question 3	Question 3	Question 3	AstraZeneca has no comments on this question at this time	Thank you.
AstraZeneca	Questions	1.2 Intervention and comparators	Question 4	Question 4	AstraZeneca believes that recommendations 1.2.2–1.2.6 are appropriate and sufficiently specific for the purpose of the obesity reference case extension. Further specification would be premature given the rapidly evolving obesity treatment landscape, with multiple therapies likely to enter and adopt different positions across populations.	Thank you for your comment.

AstraZeneca	Questions	1.4 Clinical parameters and variables (treatment effects and risk prediction)	Question 5	Question 5	AstraZeneca believes that providing a list of well-established risk tools and specifying the population strata for which each is most appropriate would improve consistency across models. When specific subgroups are considered, the use of disease-specific risk tools, for example, renal and cardiovascular risk equations can be beneficial.
					
					The list below offers examples of validated risk equations aligned to relevant population strata included in this consultation that NICE could consider:
					
					• QRISK3 (primary-prevention ASCVD)[6]
					  ○ Relevant strata: Overweight or obesity; no ASCVD at baseline; with or without T2DM
					  ○ Modelling gaps it can cover: Estimating ASCVD incidence and first cardiovascular events
						Thank you for your comment. This point is covered within our thematic response to related comments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					○ Limitations: Not suitable for secondary prevention; largely cross-sectional inputs with limited capture of BMI history; potential miscalibration in subgroups without local validation • QR4 (primary-prevention ASCVD)[7] – accounts for wider range of risk factors compared to QRISK3 ○ Relevant strata: Overweight or obesity; no ASCVD at baseline; with or without T2DM ○ Modelling gaps it can cover: Estimating ASCVD incidence and first cardiovascular events ○ Limitations: Not suitable for secondary prevention; largely cross-sectional inputs with limited capture of BMI history; potential miscalibration in subgroups without local validation • QDiabetes (incidence of T2DM)[5] ○ Relevant strata: Overweight or obesity; no T2DM at baseline; with or without ASCVD ○ Modelling gaps it can cover: Estimating T2DM incidence;	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					transitions from normoglycaemia/prediabetes using BMI, HbA1c, blood pressure and other covariates o Limitations: Focuses on incidence rather than complications; performance can vary by ethnicity/deprivation without local validation • UKPDS Outcomes Model (T2DM complications/progression)[13] o Relevant strata (examples): Any BMI; established T2DM; with or without ASCVD o Modelling gaps it can cover: Macrovascular (MI, stroke) and microvascular complication risks; disease progression; downstream costs and utilities Limitations: Based on historical cohorts; background therapies and baseline risks may differ from current NHS	
AstraZeneca	Questions	1.8 Equality and other considerations	Question 6	Question 6	AstraZeneca has no comments on this question at this time	Thank you.
AstraZeneca	Questions	Question 7	Question 7	Question 7	AstraZeneca has no comments on this question at this time	Thank you.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Bardet-Biedl Syndrome UK	EHIA	1.1 Population	General	General	The current assessment does not reference rare genetic or syndromic obesity, despite these groups experiencing substantial inequalities linked to disability, access to care, and stigma. Including rare disease obesity within the equality considerations would strengthen the document's recognition of underserved groups.	Thank you for your comment. We recognise that a broad range of population groups may be affected by obesity, including people living with rare genetic or syndromic causes of obesity. However, as outlined in the position statement, the primary purpose of our disease-specific reference case extension is to promote consistency in health economic modelling across NICE assessments. To achieve this, reference case extensions have to focus on common diseases and conditions where multiple pieces of NICE guidance typically exist, and where standardisation can therefore provide the greatest value. We will endeavour to make this clearer in future scopes for reference case extensions. We recognise the barriers faced by people in these groups, and we have now acknowledged this in our EHIA document. We have added an acknowledgement in the reference case extension rationale and supporting information that pathways and effect sizes will be different for people with syndromic or genetic obesity.
Bardet-Biedl Syndrome UK	HE literature review	1.1 Population	General	General	The evidence base appears to focus largely on common forms of obesity and general-population evidence. This highlights an important gap in the evidence base for rare genetic and syndromic obesity, where clinical pathways and treatment responses differ	Thank you for your comment. We have now acknowledged that treatment pathways and treatment responses differ to those without the conditions in our EHIA document, and added an acknowledgement in

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					significantly. Acknowledging this gap would help ensure more equitable consideration of these groups in future modelling.	the reference case extension rationale and supporting information that treatment pathways will be different for people with syndromic or genetic obesity.
Bardet-Biedl Syndrome UK	Obesity RCE report	1.1 Population	General	General	BBS UK welcomes the development of this reference case extension and kindly asks NICE to consider explicitly recognising people living with rare genetic or syndromic causes of obesity, such as Bardet–Biedl syndrome. These conditions involve lifelong, biologically driven obesity and are often accompanied by disability, learning difficulties, and wider health inequalities, which may not be fully reflected in standard modelling approaches.	Thank you for your comment. We recognise that a broad range of population groups may be affected by obesity, including people living with rare genetic or syndromic causes of obesity. However, as outlined in the position statement, the primary purpose of our disease-specific reference case extensions is to promote consistency in health economic modelling across NICE assessments. To achieve this, reference case extensions s have to focus on common diseases and conditions where multiple pieces of NICE guidance typically exist, and where standardisation can therefore provide the greatest value. We will endeavour to make this clearer in future scopes for reference case extensions. We recognise the barriers faced by people in these groups, and we have now acknowledged this in our EHIA document.
Bardet-Biedl Syndrome UK	Workshop notes	Workshop notes	General	General	We note that rare disease and syndromic obesity perspectives were not represented in the workshop discussions. To ensure the reference case is inclusive of all	Thank you for your comment. We recognise that a broad range of population groups may be affected by obesity, including people living with rare genetic or syndromic causes of obesity.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					groups affected by obesity, we would welcome future workshops involving rare disease charities and specialist clinicians so that these experiences can contribute to model development.	However, as outlined in the position statement, the primary purpose of our disease-specific reference case extensions is to promote consistency in health economic modelling across NICE assessments. To achieve this, reference case extensions have to focus on common diseases and conditions where multiple pieces of NICE guidance typically exist, and where standardisation can therefore provide the greatest value. We will endeavour to make this clearer in future scopes for reference case extensions.
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	General	General	The document contains numerous ways in which the target population for treatment could be stratified based on baseline status. This has the potential to produce a huge number of sub-groups, each with its own incremental cost-effectiveness ratio (ICER): #1.1.1 (8 required strata) #1.1.2 (further subgrouping based on difference in baseline risk or threshold for surgery) #1.1.3 (5-level BMI categories x 2-level ethnicity) #1.3.5 (by age and sex and BMI category and comorbidities). In sensitivity analyses: #1.1.4 (by 5 additional comorbidities, in absence of T2DM and ASCVD at baseline) #1.1.5 (by 2 additional comorbidities, in presence of T2DM and/or ASCVD at baseline)	Thank you for your comment. Please see our themed response on Population: number of subgroups and Population: ASCVD as a subgroup.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					NICE final scope document refers to "*adult patients with overweight or obesity with or without pre-existing weight-related comorbidities*". The required and recommended subgroupings and stratifications will lean towards a much more restrictive scope. Recent HTA experience with PCSK9 inhibitors and hepatitis C virus medications highlights the increased complexity of introducing multiple subgroups in practice, and the risk of inequitable coverage. Finally, excessive subgrouping would also have implications for clinical trial design including the inability to power trials for all subgroups, resulting in high uncertainty and wide confidence intervals for treatment effect. We suggest considering limiting the number of required strata to a maximum of four key groups to enhance clarity of the economic assessment of AOM, prevent fragmentation of the patient population with overweight and/or comorbidities, and as such facilitate an equitable approach to population definition in obesity health economic models. Removing ASCVD stratum, while keeping T2DM as 'recommended' would be aligned with existing scientific base.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	General	General	The benefits of weight loss should be assessed across the full spectrum of obesity-related conditions (metabolic, inflammatory, mechanical, and mental health) on equal terms to ensure fair and comprehensive evaluation. We advocate for	Thank you for your comment. The list of health states is a summary of those that have been modelled and are supported by

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					inclusion of comorbidities involving inflammatory pathways (e.g., asthma, rheumatoid arthritis, psoriasis), mechanical complications (e.g., osteoarthritis, sleep apnoea), and mental health disorders (e.g., anxiety, depression). These conditions are underrepresented in previous models, despite their high prevalence and substantial impact on quality of life and healthcare resource utilisation. Younger and middle-aged patients with obesity more commonly present with dyslipidaemia, hypertension and comorbidities involving inflammatory pathways - such as asthma, psoriasis, inflammatory bowel disease (IBD), rheumatoid arthritis - as well as mental health conditions. (Bae et al., 2025; Kivimäki et al., 2022). Economic evaluations that focus predominantly on late onset comorbidities like ASCVD, T2DM, CKD, and omit broader spectrum of obesity burden, may unintentionally disadvantage younger and middle-aged individuals with obesity in terms of access to care and undervalue the broader therapeutic impact of obesity interventions. A more inclusive approach to comorbidity selection is needed to ensure equitable and comprehensive assessment across age groups. A more inclusive approach is essential to accurately capture the full morbidity burden of	evidence. They do not include every outcome that could be modelled. We have clarified the criteria for selecting outcomes, which include evidence of an association between weight loss and improved outcomes, hence there need not necessarily be direct evidence from a randomised trial. We have broadened the number of included ORCs used as suggested outcomes in the model: • Hip replacement in addition to knee replacement to cover osteoarthritis, which otherwise is mainly treated by low-cost medicines • Chronic kidney disease • Mental health care costs have been added. The evidence that you cite elsewhere (Khunti et al 2023), does not show an independent relationship between weight loss and depression. It does show an independent effect on asthma and PCOS but these outcomes are not typically included in core outcome sets for obesity treatment. The statement specifies to subgroup by type or number of obesity-related comorbidities; the

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					obesity across age groups and to support equitable access to treatment. Indirect treatment effects such as reductions in inflammatory markers (e.g., CRP), improvements in mechanical burden (e.g., weight loss), in addition to modulation of cardio-renal-metabolic risk factors contribute significantly to the overall clinical and economic value of AOMs. Recognising and appropriately evaluating these multifaceted effects is essential for accurate HTA decision-making. Besides, the rationale for the selection of the minimum set of health states versus sensitivity analyses or qualitative assessment should be strengthened, on the basis of (1) the strength of evidence there is a causative link and (2) any evidence of reversal (or reduced incidence) of the event when obesity is reduced.	conditions listed are examples and does not preclude subgrouping by other comorbidities if they can be demonstrated as being clinically or economically important.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	General	General	Use of an IPS model – would enable generation of a real-world representative cohort, and trial specific cohort to enable assessment of impact of assumption of transferability of treatment effect on economic outcomes. It will be valuable to have it discussed in the section concerning guidance on sensitivity analysis.	Thank you for your comment. We think comparing results based on the trial cohort with results based on the target population has some merit. But we are unsure how it could be used for the "assessment of impact of assumption of transferability". However, we expect that hazard ratios or the magnitude of risk factor changes like weight loss might have to be tentatively transferred between strata or subgroups in the absence of more direct evidence.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Boehringer Ingelheim Ltd	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	General	General	We suggest the following approach and hierarchy of evidence: 1) Prediction of onset of new events: T2DM, ASCVD, inflammatory diseases, mental health - all informed by risk equations or incidence risk per BMI category - this type of risk prediction can't be informed by clinical trials due to large number needed to treat (NNT), population health impact over a life long time horizon have to rely on modelling assumptions and assumptions should be equally allowed for metabolic, CV as well as a risk of onset of inflammatory conditions like (RA, Asthma. Psoriasis, OA, etc) as well as mental health. 2) Direct treatment effect on prevalent comorbidities (T2DM, ASCVD (secondary prevention), MASH, and other ORCs) - should be informed by data from clinical trials.	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	002	002	*#1.1.1 NICE requires stratification across eight strata combining overweight/obesity status with T2DM and ASCVD presence at baseline.* The rationale to require a stratified assessment by T2DM status at baseline is well understood and supported by trials design and current evidence: key trials of anti-obesity medications (AOM) were conducted separately per T2DM status (STEP-1 and -2, SURMOUNT-1 and -2, SYNCHRONIZE-1 and -2), and T2DM is an established effect modifier (Deng 2025). Nevertheless, previous health technology appraisals (HTA) for AOM excluded patients	Thank you for your response. While the company submissions excluded patients with prevalent T2DM at baseline, the committees felt that this subgroup was an important consideration as they were covered by the technology's marketing authorisation. For example, in TA875 and TA1026, the committee noted how the weight change would be different in this population, and the health gain arising from weight change would also differ, and the exclusion of T2DM from the modelled population at baseline introduced some uncertainty about the generalisability of the clinical effectiveness results, and may have affected the reliability of

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					with prevalent T2DM at baseline (TA664 of liraglutide, TA875 of semaglutide, TA1026 of tirzepatide). Assessing the subgroup of patients with T2DM at baseline in upcoming appraisals may disadvantage newly assessed treatment options by introducing additional complexity, that will be required to capture T2DM progression and complications and change in morbidity burden and risk profile not accounted for in earlier evaluations. This inconsistency could lead to inequitable comparisons and misrepresentation of relative value across interventions.	the cost-effectiveness results. Patient experts explained how separating access to new technologies for the T2DM and obesity populations could create confusion and worsen existing stigma. The committee for TA1026 concluded that it was appropriate to include people with T2DM within any population for which tirzepatide was recommended for weight management. It is important to include statements about modelling T2DM in an obesity model. A model of obesity will be required to include T2DM progression and complications, as this is a key health state in models for this population, and people who do not have T2DM at baseline may develop it as a downstream event. Furthermore, previous economic models for obesity have captured treatment pathways and progression for T2DM, and including the statements on how to model these health states is expected to result in greater consistency across appraisals, rather than reduce it.
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	002	006	*#1.1.1 NICE requires stratification across eight strata combining overweight/obesity status with T2DM and ASCVD presence at baseline.* The rationale for requiring a stratification by presence of atherosclerotic cardiovascular disease (ASCVD) at baseline is not clear: ASCVD was not assessed as a baseline characteristics in previous appraisals, is not an established treatment-effect modifier for weight-	Thank you for your comment. Please see our themed response on Population: ASCVD as a subgroup.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					loss outcomes to the best of our knowledge and is subject to standalone HTA assessment in a cardiovascular indication (ID6441, semaglutide in secondary prevention). Therefore, requiring stratified analyses by ASCVD status does not seem clinically justified. We acknowledge that a factor does not have to be a treatment effect modifier to be the basis of a sub-group. Yet, if the relative treatment effect is not modified between two groups, then the aggregated results will adequately reflect the overall baseline risk of the modelled population. From a modelling standpoint, modelling strata of patients with prevalent ASCVD at baseline will have inherited large uncertainty given scarcity of robust data in secondary prevention: the relevant treatment benefit lies essentially in the prevention of recurrent cardiovascular events. However, existing risk equations such as Q-Risk and Framingham are designed to estimate the risk of a first ASCVD event and do not enable modelling risk of recurrent events. As a result, within the current analytical framework, it is not possible to directly translate the proposed reference case benefit of weight loss (WL) in this subgroup into a quantifiable reduction in clinical outcomes, such as recurrent cardiovascular events. The only exception is the ability to model the risk of developing T2DM, as	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					this outcome remains estimable within the available scope and data constraints. We suggest removing the stratification by ASCVD at baseline from the reference case requirement, due to lack of evidence suggesting ASCVD being an effect-modifier for a weight loss.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	003	001	#1.1.3 The suggested categorisation by ethnicity may be impractical in the context of obesity modelling, as ethnicity is already embedded within cardiovascular, renal, and metabolic risk equations - alongside BMI - as a direct modifier of risk. In these cases, stratification by ethnicity is inherently accounted for. We propose to rephrase and ask to present results by classes that are meaningful for each ethnicity. But different thresholds cannot coexist when using BMI distribution estimates per class.	Thank you for your comment. Ethnicity-specific categorisation of BMI category was included in the statement to capture that people in these ethnic categories have a higher cardiometabolic risk at lower BMI levels compared to those who are not in these categories. The rationale for selecting subgroups was to present cost-effectiveness results for those who are at equivalent risk of experiencing each event. Therefore, it is *because* risk equations include ethnicity that we want to define the BMI-related categories for subgrouping in this way.
Boehringer Ingelheim Ltd	Obesity RCE report	1.1 Population	003	006	#1.1.6 Including a healthy weight category in obesity models may add value by enabling the application of relative risks (RR) or odds ratios (OR) for outcome events across weight categories, benchmarked against individuals with normal weight. This approach allows for a more nuanced and clinically relevant estimation of risk, reflecting the of disease burden associated with BMI.	

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Boehringer Ingelheim Ltd	Obesity RCE report	1.2 Intervention and comparators	004	022	#1.2.4 While bariatric surgery is a relevant and important comparator in obesity treatment evaluations, there is a notable lack of large-scale clinical trials comparable to those conducted for AOMs. Long-term data on outcomes such as weight loss and weight regain trajectories are limited and often derived from single-centre cohort studies, which may not be generalisable. This evidence gap poses challenges for robust comparative modelling. Incorporating bariatric surgery as a comparator also requires accounting for procedure-specific complications, such as peritonitis, sepsis, anastomotic or sleeve stenosis, intestinal obstruction, and perioperative mortality. Excluding these risks - particularly those that necessitate revision surgery, prolonged hospitalisation, intensive care, or increase the risk of death - may introduce information bias and distort the overall cost-effectiveness assessment.	Thank you for your comment. The inclusion of bariatric procedures as a comparator has been kept in the reference case extension as it is a relevant treatment option and reflects the existing NICE obesity guideline. Procedure related adverse events are now explicitly included (see sections on model structure, quality of life and costs) in the reference case extension where applicable.
Boehringer Ingelheim Ltd	Obesity RCE report	1.2 Intervention and comparators	005	014, 018	#1.2.8 Testing different intensities of behavioural interventions is currently impractical due to the lack of data on how intervention intensity or setting (e.g., GP office vs. specialised centre) impacts clinical outcomes. In the absence of robust evidence, models can only reflect differences in cost, while assuming no variation in effectiveness. New data collection on behavioural intervention characteristics is	Thank you for your comment. Yes, these sensitivity analyses would only change costs and not treatment effects due to lack of data, which is a limitation however understanding the impact on costs is still useful.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					needed to support more nuanced modelling in the future.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	006	008	Cohort models are not capable of accommodating all the "required" specifications for evaluating obesity interventions, particularly when individual-level heterogeneity and broad range of comorbidities. It is therefore unclear why cohort modelling is recommended. An oversimplified model structure requires accommodation of strong assumptions, that may limit comparability of outcomes vs cases utilising IPS technique. An analogy can be seen with Lupus (SLE) and the risk of organ damage, which was modelled using nine organ-specific risk equations mediated by changes in disease activity scores (NICE TA 752 of belimumab).	Thank you for your comment. We agree that cohort models are challenging in this area but it's not impossible to overcome the limitations. We also offer the option of IPS modelling.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	007	003	*#1.3.6 NICE guidelines restrict health states to a minimum set of complications for patients without T2DM nor ASCVD at baseline: T2DM, ASCVD as health states, plus obstructive sleep apnea (OSA), total knee replacement (TKR), and bariatric procedures as health events.* The step towards expanding obesity-related complications (ORCs) beyond the scope of incident T2DM and ASCVD is positive and welcome in the reference case. As such, the inclusion of OSA and TKR as health events is relevant, in line with previous appraisals (TA875 of semaglutide, TA1026 of tirzepatide). However, in the framework of a disease-specific reference case, the currently selected ORCs	Thank you for your comment. The list of health states is a summary of those that have been modelled and are supported by evidence. They do not include every outcome that could be modelled. We have broadened the number of included ORCs used as outcomes in the model: • Hip replacement in addition to knee replacement to cover osteoarthritis, which otherwise is mainly treated by low cost medicines • Chronic kidney disease

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					only offers a partial view of the actual scope, burden and complexity of overweight/obesity. Obesity is a chronic, relapsing disease associated with a wide range of comorbidities and complications, including mechanical effects, cardiometabolic and inflammatory conditions, and significant mental health impacts (Bae et al. 2025). In the Global Burden of Disease (GBD) 2023 study, obesity/overweight was listed among the top five risk factors to be addressed to potentially halve the number of healthy years lost each year globally. From the perspective of the United Kingdom (UK) National Health Services (NHS), fighting obesity appears in the main objectives of the NHS 10-year plan. The 10-year plan states that "*Obesity is one of the leading causes of poor health*". 'Poor health' cannot be limited to T2DM, ASCVD, OSA and TKR (one time off procedure). We would therefore advocate for an expanded, evidence-based scope of comorbidities in obesity models, specifically recommending the inclusion of inflammatory (asthma, rheumatoid arthritis), mental health (depression), and mechanical conditions (osteoarthritis), as well as chronic kidney disease (CKD) in the scope of recommended health care states. The cost of treating ORCs beyond T2DM and ASCVD is not negligible, considering new	The evidence that you cite (Khunti et al 2023, does not show an independent relationship between weight loss and depression. It does show an independent effect on asthma and PCOS but these outcomes are not typically included in core outcome Sets for obesity treatment.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					expensive drugs in severe asthma, PCSK9 in dyslipidemia, biologics in moderate-severe inflammatory diseases like rheumatoid arthritis (RA). Beyond the missed burden and morbidity, the rationale for including OSA and TKR and not asthma, depression or osteoarthritis (OA) for example, is not clear: Looking at ORC prevalence ranges in obesity classes 1-3 in the UK primary care database analysis of Khunti et al. (2023): - OSA prevalence at baseline (0.9-3.3%) is minor compared to that of asthma (16.2-21.5%) and depression (12.0-17.0%). - Hip/knee osteoarthritis (OA) concerns 5.8-7.3% of patients at baseline: only accounting for the fraction of patients eventually receiving joint replacement means that years of OA morbidity and treatments costs will be lost. - Hypertension (50.8-54.9%) and dyslipidemia (42.6-38.5%), with about half of the population concerned at baseline, should be studied upfront in any health economics model of overweight/obesity. Reasons not to add further ORCs (including reproductive health, mental health, chronic lower back pain and inflammatory conditions including	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					arthritis) were listed on page 25, line 9. We would like to share the below comments, and ask NICE to reconsider/rephrase the proposed reasons for rejecting most ORCs: - *"insufficient direct evidence of treatment effect"* It would be beneficial to clarify that benefits of weight loss should be enabled in the reference case. There is sufficient literature demonstrating a statistically significant association between weight loss/effective weight management and reduced risk of developing ORCs (for example, depression and severe asthma) in patients without the condition at baseline. The nature of this assumption and its evidence base are consistent with the current reference case assumptions for reducing the risk of ASCVD or T2DM in patients without these conditions at baseline. Importantly, our suggestion is different from recommending the use of GLP-1s in patients with prevalent ORC or claiming any improvement in ORC state during treatment. What we do suggest is that effective weight management in patients without prevalent ORC can help reduce the risk of developing these conditions, based on the well-documented relationship between body weight and ORCs in the literature. Direct evidence beyond weight loss is indeed something to be demonstrated via specifically	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					designed trials (requiring a large number of patients). - *concerns with the potential for modelling complexity and double counting of impact on quality of life.* By using a patient-level simulation model (IPS), these hurdles can be largely overcome. Risk of costs and QoL double counting can be controlled via different techniques, and in a conservative way. - *additional health outcomes could be captured qualitatively.* The proposed qualitative assessment adds complexity and the methodology remains unclear. Most likely underlying quantification and calculations are required to obtain a qualitative assessment and relevant conclusions. - *However, if new direct evidence of treatment effect emerges to warrant their inclusion, then they can be considered for inclusion within the reference case extension.* Direct treatment evidence beyond the benefit of weight loss is only available for (recurrent) ASCVD. Based on this rationale, ORCs such as OSA and TKR should also not be present in the minimum set. Overall, we believe that the risk of onset of broad spectrum of comorbidities in patients with obesity should be addressed in obesity models,	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					as chronic disease modelling requires accounting for lifetime effects, including costs, quality of life, and quality-adjusted life-years (QALYs). Finally, current document appears to lack transparent, clinically justified selection process and we wanted to highlight the limitations and equity concerns of the current NICE proposal.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	007	018	*#1.3.7 For patients with ASCVD and/or T2DM at baseline, it is recommended to further include the two health states CKD and CHF.* The prevalence of obesity has been shown to directly elevate the risk of developing CKD, independently of T2DM or ASCVD (Nawaz et al., 2022). This relationship is partly attributed to obesity-related glomerulopathy, where excess body weight contributes to structural changes in the kidneys themselves. Histopathological findings support this direct link, indicating that the impact of obesity on kidney health is not solely mediated by other metabolic or cardiovascular conditions. Validated risk equations exist, including a model published by Nelson et al. (2019), that incorporates BMI as a standalone risk factor for the development of CKD in the general population. Hypertension is recognised as the second major cause of CKD, along with T2DM. Individuals with	Thank you for your comment. We initially restricted CKD status to cohorts with T2DM or ASCVD, on the basis that some existing models did not include CKD and the incidence of CKD is likely to be lower. However, for clarity, we have recommended that CKD/CHF be included for all strata.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					obesity are at heightened risk of developing hypertension earlier in life, due to both prolonged exposure and the high prevalence of high blood pressure in this population. This risk persists even in the absence of T2DM or ASCVD, suggesting that obesity alone is a critical driver of CKD risk. Young and middle-aged individuals with obesity are particularly vulnerable. The early onset of hypertension (Bae et al., 2025) and the direct impact of obesity on kidney function contribute to this elevated lifetime risk of developing CKD, highlighting the importance of capturing CKD complication across all strata. We propose therefore to capture the risk of CKD regardless of the baseline T2DM and ASCVD status in the reference case. This risk should be appropriately reflected in the estimated lifelong morbidity burden of obesity, regardless of whether a direct treatment effect on kidney function decline (via eGFR) is claimed.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	007	024	#1.3.8 It is currently unclear what constitutes progression of T2DM status within the model. Is progression intended to reflect movement across treatment lines, worsening glycaemic control, development of complications, or another dimension? Given the chronic and progressive nature of T2DM, it is essential that models with a lifelong time horizon capture both the clinical and economic implications of disease progression. This includes increasing complexity	Thank you for your comment. We have now clarified that we mean progression from 'normoglycaemia' to 'non-diabetic hyperglycaemia' to 'diabetes'. For strata without diabetes at baseline, this should be sufficiently complex. Unit costs and utility decrements based on weighted average of treatments could then be applied.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					of treatment regimens, higher risk of comorbidities, and escalating healthcare resource utilisation over time. Clear guidance is needed to define progression criteria and ensure consistent, clinically meaningful representation of T2DM in economic evaluations.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	008	018	*#1.3.11 In sensitivity analyses, it is recommended to add further health events if there is direct evidence of a treatment effect: MASLD, cancer (breast, colorectal, kidney, liver, womb), CKD.* We value the extension of the scope to these additional, established ORC in sensitivity analyses, but would expect to see more clarity / precision concerning the type of "direct evidence" required: As also mentioned in the Workshop notes (page 2, line 10), the separation should appear more clearly between treatment benefit of weight loss itself, and drug specific treatment effect beyond weight loss - the former should be considered across broad morbidity spectrum, while evidence should come from clinical trials for the latter - and can vary across future products. Some health benefits of GLP-1 therapy, such as improved liver and kidney function, may result from weight loss rather than unique drug effects. It's important to distinguish between benefits from weight loss (or improvement of other surrogate endpoints) and those from	Thank you for your comment. Since treatment effects can be greater or less than that predicted by weight alone, in the revised reference case extension we have emphasised the use of direct treatment effects over risk equations.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					pharmacological action. GLP-1 drugs are also being explored for treating conditions driven by inflammation or other non-obesity factors, where they appear to have direct, weight-independent therapeutic effects (such as reducing inflammation, protecting against neurodegeneration, and influence hormone production) (Lin et al. 2025, Xie et al. 2025, Mackenzie et al., 2025). The class of AOM is closer to being "disease-modifying agents" than "lifestyle medications" (Holownia 2025) and this also supports the inclusion of a broad range of conditions.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	010	002	*#1.4.4 The selection of validated risk prediction tools or risk equations to estimate modelled outcomes and events should be justified. (required)* Clearer guidance on the criteria for what constitutes a "justified" assumption would be highly beneficial. In the absence of specific standards, there is a risk of arbitrary judgments that may impact the consistency and fairness of the evaluation process. Recent experience with NICE Early Advice has shown that commonly accepted arguments - such as prior use in similar cases or alignment with clinical guidelines - were deemed insufficient by NICE advisors. This highlights the need for transparent and standardised criteria to support applicants in developing robust submissions.	Thank you for your comment. This point is covered within our thematic response to related comments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					We suggest NICE explicitly allows the use of validated risk equations, surrogate outcomes, and high-quality real-world evidence for modelling the benefits of weight loss in obesity, while reserving the requirement for direct trial evidence for drug-specific effects.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	005	#1.5.1 Assuming consistent weight trajectories across different interventions is not clinically justified. Behavioral interventions typically result in more gradual and plateauing weight loss, whereas AOMs can produce more pronounced and steep weight decline, the trajectory may vary across different mechanisms of action. To accurately reflect treatment benefit, economic models should allow for variability in weight trajectories across interventions, rather than applying a uniform assumption. This approach ensures a more realistic representation of clinical outcomes and supports robust health economic evaluations.	Thank you for your comment. The statement has been revised.
Boehringer Ingelheim Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	013	#1.5.1 Assuming a uniform pattern of weight regain following treatment discontinuation is not clinically justified. Evidence from real-world studies, such as the Look AHEAD trial (Liu et al. 2022), demonstrates that weight regain trajectories vary significantly across individuals, particularly depending on the magnitude of initial weight loss (e.g., ≥5%). This heterogeneity should be reflected in economic models to accurately capture the treatment benefit. Allowing for variability in post-treatment weight	Thank you for your comment. We have revised the statement.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					regain is essential to avoid underestimating long-term outcomes and to ensure an adequate representation of therapeutic impact.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	013	001	*#1.5.8 Ideally mortality rates should be specific to both the health state and the body mass index (BMI) category. However, if specific data is not available then either apply BMI-adjusted all-cause mortality ratios or condition specific mortality ratios (but not both). (required).* Assumptions on mortality have a major impact on life-years, QALYs and thus ICER. A consistent and transparent approach would support methodological alignment across HTA submissions, reduce variability in modelling practices, and enhance comparability of results across therapeutic interventions. Would it be possible for NICE to give more detailed guidance on the required approach (e.g., eligible sources of data, or risk equation to link mortality to BMI)?	Thank you for your comment. Please refer to the thematic response "mortality".
Boehringer Ingelheim Ltd	Obesity RCE report	1.7 Cost and healthcare resource use identification, measurement and valuation	015	012	*#1.7.6 Recommending to use UKPDS, which include the cost of consultations, visits, admissions and procedures associated with diabetes-related complications. (recommended)"* Patients with prevalent T2DM often require treatment intensification and are at risk of experiencing a wide range of complications including hypoglycaemia, blindness, ulceration, lower limb amputation, ASCVD, heart failure, and chronic kidney disease. Many of these	Thank you for your comment. The UKPDS (Alva 2015) includes the following seven complications: myocardial infarction, ischaemic heart disease, stroke, heart failure, amputation, cataract extraction and blindness in one eye. Using this source for the weighted average costs associated with T2DM management and complications would therefore capture the costs associated with these long-term complications. In addition, average T2DM EQ-5D estimates could potentially capture these complications.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					complications are complex conditions in their own right. Is the use of UKPDS source compatible with the modelling of above-mentioned T2DM long-term complications? In the context of NICE Early Advice, feedback received by the company indicated that inclusion of severe diabetes-related complications such as blindness and lower limb amputation, was deemed unjustified within an obesity model. If this approach is followed, it may significantly undermine the perceived benefit of chronic weight management over a lifetime horizon. This is particularly concerning given that many patients with obesity are relatively young and, over time, are at substantial risk of developing severe T2DM-related complications.	
Boehringer Ingelheim Ltd	Obesity RCE report	1.8 Equality and other considerations	016	004	*#1.8.2 It is recommended to consider qualitatively the impact of AOM on: costs and HRQoL beyond trial follow-up associated with mental illness, for example, depression and anxiety.* Capturing the impact of clinical depression only "qualitatively" introduces bias in estimating the true morbidity burden in patients with obesity. The GBD study 2023 highlighted a sharp increase in healthy years lost due to non-communicable diseases between 2013 and 2023, citing anxiety and depressive disorders among the three drivers (with diabetes).	Thank you for your comment. We agree that mental health should be modelled but do not agree that it is necessary to have specific mental health states in the model. The methods suggested for calculating utility by weight and comorbidity should adequately account for mental health. Similarly, we have proposed that mental health costs also be captured within health state costs if possible.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Depression is a serious clinical condition requiring long-term management, including regular psychotherapy sessions and psychiatric follow-up. In the UK, the NHS faces significant resource constraints in meeting the growing demand for mental health services, resulting in prolonged waiting times for care even for patients at increased risk of suicidality. The bidirectional relationship between obesity and mental health disorders must be robustly modelled in the context of chronic weight management to accurately quantify the therapeutic impact on this highly prevalent comorbidity. This is particularly important given its substantial contribution to healthcare resource utilisation (HCRU) within the NHS. We propose to reconsider the status of mental illness in health economics models of obesity, and move "depression" from the 'qualitative assessment' recommendation to the 'minimum set of heath states'. Risk models exist and can be used to implement the risk of developing depression as a function of BMI level (e.g., Moussah et al. 2019)	This means that it has now been lifted out of the qualitative section.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	022	007	*Inclusion of carefully selected set of comorbidities and health events that reflect the burden of obesity should be guided by the following criteria: "availability of sufficient data to support inclusion without relying on speculative assumptions"*	Thank you for this comment. This point is purely one of pragmatism. If there are no data available for the stratum then developers should not feel compelled to include a specific outcome, just because it is in the reference case extension or a core outcome set, etc. We hope the new wording is clearer. Also, note that this paragraph

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					It would be helpful to have clarification of what constitutes "sufficient data to support inclusion without relying on speculative assumptions". In the absence of clear criteria there is a risk of misjudgement of "speculative assumption" driven by lack of understanding of the morbidity burden in obesity population. For example, evidence of improvement of clinical course and treatment response in patients with obesity and asthma, or patients with obesity and rheumatoid arthritis if they are able to achieve meaningful weight loss, informed by real-world evidence (RWE) can get wrongly labelled as a "speculative assumption".	has been promoted to the main part of the reference case extension.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	022	009	*Inclusion of carefully selected set of comorbidities and health events that reflect the burden of obesity should be guided by the following criteria: "evidence of it having a meaningful impact on costs, quality of life or risk of other outcomes (for example, mortality)"* It would be helpful to have clarification of what constitutes "evidence of it having a meaningful impact on costs, quality of life or risk of other outcomes".	Thank you for your comment. It's not possible to give a threshold on what counts as a meaningful difference vs a negligible one. We expect a reasoned argument from model developers.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	022	016	We believe there are inconsistencies across the document concerning what is accepted as evidence or not: risk equations are accepted for ASCVD and T2DM without direct trial evidence, but not for other non-CV complications, despite validated models of weight-loss benefits being available. Of which (non-exhaustive list):	Thank you for your comment. We have made the document more consistent in terms of acceptable evidence. In general we have now acknowledged that multivariate analyses that show an independent association between weight

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					- Inflammatory conditions: Asthma (Hjellvik et al., 2010), Rheumatoid arthritis (RA) (Ljung et al., 2016), Crohn's disease (He et al., 2023) - Mental health disorders: Clinical depression (Moussa et al., 2019) - Mechanical complications**:** Low back pain (Shiri et al., 2019), Obstructive sleep apnoea (OSA) (Erridge et al., 2021), Osteoarthritis (OA) (Maki et al., 2024); knee and hip replacement due to OA (Apold et al., 2014 and 2011), Lumbar radicular pain (Shiri et al., 2019) Cardiometabolic conditions: Type 2 diabetes (T2DM) (Hayes et al., 2013), Hypertension (HTN) (Parikh et al., 2008), Dyslipidaemia (DLD) (Liu et al., 2021), History of cardiovascular disease (CVD) (Hippisley-Cox et al., 2017), Chronic kidney disease (CKD, across KDIGO stages) (Nelson et al., 2019), Metabolic dysfunction-associated steatohepatitis (MASH), Metabolic dysfunction-associated steatotic liver disease (MASLD) (Le et al., 2025), Gout (Maki et al., 2024).	reduction and improvement in an outcome are acceptable, in addition to (randomised or non-randomised) evidence for specific treatments.
Boehringer Ingelheim Ltd	Obesity RCE report	1.3 Model structure and health states	022	016	*"Only events or outcomes that have been directly measured or where there are validated risk equations should be included"* Restricting inclusion to only directly measured outcomes disadvantages patients with common but under-researched comorbidities, potentially limiting their access to treatment. This approach	Thank you for your comment. We have expanded this to include outcomes where there is shown to be a statistically independent effect of weight loss with an improvement in that outcome.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					risks underestimating the true morbidity burden of obesity, particularly in populations where relevant complications (though prevalent) have not been prioritised for clinical development by pharmaceutical companies due to considerations other than the lack of clinically plausible therapeutic benefit: anticipated criticism for having too many secondary endpoints, burden imposed on patients by having to undergo multiple assessments at each clinic visit (multiple questionnaires to screen for depression, gout, OSA, etc.), budget considerations.	
Boehringer Ingelheim Ltd	Questions	1.4 Clinical parameters and variables (treatment effects and risk prediction)	Question 5	Question 5	*Would it be helpful to recommend specific risk tools / equations in this reference case extension, if yes, which ones and why (see 1.4)?* Yes we believe that recommendations of eligible risk prediction tools for (BMI-adjusted) general and/or cardiovascular mortality would be beneficial, as well as eligible models of MAFLD risk progression that connect independent risk factors.	Thank you for your comment.
Boehringer Ingelheim Ltd	References	General	References	References	Apold, H., Meyer, H. E., Espehaug, B., Nordsletten, L., Havelin, L. I., & Flugsrud, G. B. (2011). Weight gain and the risk of total hip replacement a population-based prospective cohort study of 265,725 individuals. *Osteoarthritis and cartilage*, *19*(7), 809-815.	Thank you for providing these additional references to support your comments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
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Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
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Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					lifestyle medicines? Reframing the policy and economic debate. *Certara*. PowerPoint Presentation Institute for Health Metrics and Evaluation (IHME). (2025). *Global Burden of Disease 2023: Findings from the GBD 2023 study*. Seattle, WA: IHME. https://www.healthdata.org/sites/default/files/2025-10/GBD_2023_Booklet_Final_2025.10.17.pdf Kivimäki, M., Strandberg, T., Pentti, J., Nyberg, S. T., Frank, P., Jokela, M., Ervasti, J., Suominen, S. B., Vahtera, J., Sipilä, P. N., Lindbohm, J. V., & Ferrie, J. E. (2022). Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study. The lancet. Diabetes & endocrinology, 10(4), 253–263. https://doi.org/10.1016/S2213-8587(22)00033-X Le, P., Tatar, M., Dasarathy, S., Alkhouri, N., Herman, W. H., Taksler, G. B., ... & Rothberg, M. B. (2025). Estimated Burden of Metabolic Dysfunction–Associated Steatotic Liver Disease in US Adults, 2020 to 2050. *JAMA Network Open*, *8*(1), e2454707-e2454707. Lin, H. T., Tsai, Y. F., Liao, P. L., & Wei, J. C. (2025). Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity. *JAMA network open*, *8*(7),	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					e2521016. https://doi.org/10.1001/jamanetworkopen.2025.21016 Liu, N., Birstler, J., Venkatesh, M., Hanrahan, L., Chen, G., & Funk, L. (2021). Obesity and BMI cut points for associated comorbidities: electronic health record study. *Journal of medical Internet research*, *23*(8), e24017. Liu, M et al. (2022). Cardiovascular effects of intensive lifestyle intervention in adults with overweight/obesity and type 2 diabetes according to body weight time in range. eClinicalMedicine, Volume 49, 101451. Ljung, L., & Rantapää-Dahlqvist, S. (2016). Abdominal obesity, gender and the risk of rheumatoid arthritis–a nested case–control study. *Arthritis research & therapy*, *18*(1), 277. Mäki, P., Harald, K., Lindström, J., Männistö, S., & Laatikainen, T. (2024). Association of adiposity with morbidity in Finnish adults: A register-based follow-up study. *Scandinavian Journal of Public Health*, *52*(4), 461-467. Moussa, O. M., Ardissino, M., Kulatilake, P., Faraj, A., Muttoni, E., Darzi, A., ... & Purkayastha, S. (2019). Effect of body mass index on depression in a UK cohort of 363 037	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
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Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Journal of Human Pharmacology and Drug Therapy, *45*(3), 177-186. Shiri, R., Falah-Hassani, K., Heliövaara, M., Solovieva, S., Amiri, S., Lallukka, T., ... & Viikari-Juntura, E. (2019). Risk factors for low back pain: a population-based longitudinal study. *Arthritis care & research*, *71*(2), 290-299. Xie, Y., Choi, T., & Al-Aly, Z. (2025). Mapping the effectiveness and risks of GLP-1 receptor agonists. *Nature medicine*, *31*(3), 951-962.	
Boston Scientific Corporation	Obesity RCE report	General	General	General	General Presentation and Clarity The rationale sections (particularly for 1.2 and 1.3) could include short "examples of current NHS practice" subsections to guide consistent model construction. **Proposed addition**: We suggest that NICE consider developing worked examples, default comparators and model templates to streamline adoption of the reference case across guidance programmes (Medicines Evaluation, HealthTech, Guidelines). Clear delineation of "required" vs "recommended" elements – alongside curated links to high-value national databases (e.g. National Bariatric Surgery Registry, National	Thank you for your comments. We have now included some statements for further research to support economic modelling and evaluation of obesity treatments, and this includes potential suitable sources of data to inform future research (which includes examples of relevant national databases). We will consider worked examples as part of ongoing implementation activities. Regarding model templates, following the publication of our position statement on the use of reference models, this is an area that we will continue to explore and monitor opportunities for collaboration. We will be considering developing an obesity reference model in the future when determining the priorities for our workstream.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Obesity Audit) would further support timely implementation. Additionally, prioritised research could strengthen future methodological consistency including: (i) modality-specific long-term weight trajectories (ii) longitudinal risk models incorporating duration of obesity (iii) enhanced registry linkage for validation (iv) real-world behavioural and resource use patterns (v) standardised utility datasets (vi) improved quantification of indirect costs and recovery impacts across modalities. Collectively, these additions could enhance the usability, adaptability, and methodological robustness of the reference case as innovation evolves.	The obesity reference case extension contains statements for default comparators for evaluations in the section on comparators.
Boston Scientific Corporation	Obesity RCE report	Overview	001	006	Overview We recommend inclusion of a statement acknowledging the need to flexibly accommodate emerging technologies and hybrid care pathways that may not neatly fit existing behavioural, pharmacological, or surgical categories. This would ensure the reference case remains adaptable to ongoing innovation within NHS obesity management services,	Thank you for your comment. The terminology used throughout this reference case extension is typically broad to accommodate future developments. We do not think such a statement is necessary.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					particularly as procedural and digital therapeutics evolve.	
Boston Scientific Corporation	Obesity RCE report	1.2 Intervention and comparators	004	026 – 028	Section: 1.2 – Intervention and Comparators Section 1.2 currently references digital technologies but could clarify proportionality. Digital products should meet the same principles as medicines and other comparators but with proportionate evidence requirements reflecting shorter evaluation horizons and evolving endpoints. Proposed Addition: Clarify core requirements (validated risk tools, outcome linkages, utilities) that would apply. As evidence and horizons often differ for digital, specify proportionate depth with clear calibration/validation to England populations	Thank you for your comment. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.
Boston Scientific Corporation	Obesity RCE report	1.1 Population	002 – 003	003	Population The draft emphasises stratification by type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). However, subgroup definitions could be expanded to reflect metabolic risk heterogeneity within "non-T2DM/non-ASCVD" populations and to capture real-world variation in BMI thresholds by ethnicity. **Proposed change/Suggested addition:** To enhance the clarity and alignment with NICE guidance, we suggest three refinements:	Thank you for your comment. The reference case extension already includes statements on BMI categories by ethnicity. Waist to height ratio is clinically useful measure, especially for those with BMI below 35; however, it is less useful for modelling obesity as it is not a factor in risk equations to predict future events. Patient experts in our workshops also advised that this was less acceptable form of measurement in the general population due to its invasiveness and there is often variability between measurers, and so statements for

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					1. Explicit recognition of metabolic syndrome and insulin resistance phenotypes We recommend explicitly recognising metabolic syndrome and insulin-resistance phenotypes (without overt T2DM) as relevant subgroup characteristics, given their prognostic and economic implications and their inclusion would support more accurate modelling of early metabolic risk, disease progression and prevention benefits. Reference for ethnicity-specific BMI thresholds: NICE CG189 and subsequent updates highlight the need for lower BMI thresholds in certain ethnic groups (e.g. South Asian, Chinese, Middle Eastern, Black African), as risks occur at lower BMI values than in white populations. International consensus from WHO expert consultation (2004) also supports ethnicity-adjusted BMI thresholds for cardiometabolic risk. 2. Inclusion of waist-to-height ratio as a sensitivity measure In addition to BMI categorisation table (page 3), we suggest cross-referencing waist-to-height ratio thresholds as a secondary sensitivity measure. This is consistent with existing NICE clinical guidance and reflects current clinical practice, improving the precision of risk stratification and prevention modelling. 3. Inclusion of non-surgical patients when stratifying BMI categories	technologies made for subgroups defined on this basis may be less implementable in practice. We have updated the statement to refer to bariatric procedures, which incorporate the bariatric surgery and the procedures that are described in NICE IPGs. We have updated our statements to include metabolic syndrome in the list of potential subgroups to include in an evaluation.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					In line with populations described in NICE IPG pathways, we suggest that BMI-based stratification explicitly include non-surgical populations, not only bariatric-eligible cohorts. This supports more representative modelling of the full obesity-care continuum and aligns with real-world NHS patient flows.	
Boston Scientific Corporation	Obesity RCE report	1.3 Model structure and health states	006	007	Section 1.3 – Model Structure and Health States The proposed structure is methodologically sound but could benefit from a clearer expectation around multi-modality and sequencing between pharmacotherapy, ESG and surgery. **Suggested addition:** We suggest that section 1.3 explicitly encourage modelling of sequential or combination therapy pathways using generic, modality-neutral examples that reflect the stepwise approaches increasingly observed across obesity management. Illustrative pathways could include transitions between behavioural interventions, anti-obesity medicines, minimally invasive endoscopic procedures, and bariatric surgery. These examples are intended solely to demonstrate how models should accommodate multiple intervention sequences, rather than to recommend specific clinical pathways. This approach ensures the reference case remains flexible, methodologically consistent, and capable of representing the full range of	Thank you for your comment. We are glad you agree with the model structure. We think that the reference case extension has sufficient detail about comparators including acknowledging that comparators are often complex interventions, for example medicines should be provided along with behavioural interventions and sometimes digital technologies. Comparison of sequences can be difficult to interpret. We do not think that there is a strong case for explicitly recommending them. However, we do not exclude them and make reference to 'lines of therapy (where applicable)'. Furthermore, we do recommend that bariatric procedures averted (including minimally invasive procedures) be captured in the model.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					configurations used in NHS practice and future care models.	
Boston Scientific Corporation	Obesity RCE report	1.2 Intervention and comparators	004 – 005	009	Section 1.2 – Intervention and Comparators Section 1.2 provides comprehensive guidance on surgical and behavioural comparators but does not explicitly reference minimally invasive endoscopic interventions such as **Endoscopic Sleeve Gastroplasty (ESG).** ESG has been assessed by NICE (IPG783) and described by the NICE Chief Medical Officer as "a welcome new option" for individuals who may not wish to, or be eligible for, traditional bariatric surgery. Specifying appropriate comparators, as in paragraphs 1.2.2–1.2.6, is helpful for consistency provided flexibility is maintained through sensitivity analyses **Proposed change / Suggested addition:** We recommend that Section 1.2 explicitly acknowledge minimally invasive endoscopic bariatric interventions, such as endoscopic sleeve gastroplasty (ESG), within the scope of relevant comparators, in line with NICE IPG783. ESG represents a clinically relevant option for adults with obesity who may not meet criteria for bariatric surgery or prefer a less invasive approach. Its inclusion within the reference case would support more representative modelling of NHS obesity-care pathways, particularly for populations with obesity but without T2DM or ASCVD.	Thank you for your comment. An edit has been made to remove the example of gastric bypass after "bariatric procedures established in NHS clinical practice" from the statement as this is not the most common procedure currently. Instead, a sentence has been added to the rationale to highlight that the sleeve gastrectomy and Roux-en-Y pass are the most common procedures in NHS currently according to the National Obesity Audit – Bariatric surgical procedure dashboard. It is considered important that any new bariatric procedure is compared to bariatric procedures established in NHS clinical practice. ESG is not currently established in NHS practice. A sentence acknowledging minimally intensive endoscopic bariatric interventions has been added to the rationale, with reference to the IPG (now HealthTech guidance 711).

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					ESG should be incorporated within model structures and sensitivity analyses to allow appropriate comparison of cost-effectiveness across intervention intensities, reflecting its distinct procedural profile, safety characteristics, uptake dynamics, and commissioning considerations. To reflect evolving NHS practice, we also recommend that the reference case clarify the role of ESG and similar procedures within the continuum between pharmacological and surgical care. **Supporting evidence:** Comparative data reinforce ESG's clinical relevance as a modelling comparator. • Large meta-analysis (2022; n =6,775) comparing ESG (n = 3,413) with laparoscopic sleeve gastrectomy (LSG; n = 3,362) • Adverse events: ESG showed a lower incidence of adverse events (RR 0.51, 95% CI 0.23–1.11) and • GERD outcomes: Significantly fewer new-onset gastro-oesophageal reflux disease (GERD) cases (1.3% vs 17.9%, RR 0.10, 95% CI 0.02–0.53) • Weight loss: ESG achieved clinically meaningful total body-weight loss - ≈ 16 % at 6 months; ≈ 18 % at 12 months)	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					• Procedural characteristics: ESG is associated with fewer complications, shorter procedural times, and faster recovery • Return to work: Patients typically return to work within days rather than weeks, highlighting its relevance as an intermediate-intensity intervention These findings indicate that ESG provides an intermediate-intensity, cost-effective option between pharmacotherapy and bariatric surgery and support its inclusion as a comparator in scenario and sensitivity analyses, particularly for Tier 3 populations (BMI 30–40 kg/m²) underserved by current surgical pathways. (Beran A, Matar R, Jaruvongvanich V, Rapaka BB, Alalwan A, Portela R, et al. Comparative effectiveness and safety between endoscopic sleeve gastroplasty and laparoscopic sleeve gastrectomy: a meta-analysis of 6775 individuals with obesity. *Obes Surg*. 2022;32(12):4567–4578.) While the illustrative evidence provided relates to surgical comparators, our intention is not to limit modelling to ESG vs surgery alone. Instead, we note that the **reference case should be designed to support comparison across the full spectrum of obesity interventions**, including: • Lifestyle-based and behavioural interventions	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					• Anti-obesity medicines (AOMs) • Minimally invasive endoscopic procedures • Bariatric surgery • Sequential or combination pathways, which may become increasingly common in NHS practice This is consistent with the purpose of the reference case — to ensure methodological consistency across interventions, rather than to evaluate any specific technology. Our examples are therefore illustrative, not exhaustive.	
Boston Scientific Corporation	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	002	Section 1.4 – Clinical Parameters and Risk Prediction The draft could emphasise the need for up-to-date, intervention-specific calibration of risk equations and inclusion of procedural outcomes where available. We also support inclusion of preferred, validated risk tools—such as QRISK3, UKPDS-OM, and FRAX - with calibration guidance for English populations, to strengthen methodological consistency. **Suggested addition:** We suggest inclusion of a statement encouraging calibration of risk equations using real-world or registry data for endoscopic and surgical interventions. This would enhance model validity and support equitable comparison across procedural and pharmacological options. Early NHS experience demonstrates that ESG can be incorporated into existing registry data	Thank you for your comment, and we value your suggestions. Regarding the use of risk equations/tools and their calibration, please see our thematic response document.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					collection frameworks (for example, the National Bariatric Surgery Registry and National Obesity Audit). At Darlington Memorial Hospital, ESG achieved mean TBWL of 17.8 %, 36 %, and 26.7 % at 6, 12, and 24 months, respectively, with no major complications. This demonstrates feasibility, durability of outcomes, and a favourable safety profile in routine NHS practice, aligning with the draft's emphasis on using validated real-world evidence to inform modelling parameters. These findings highlight the value of incorporating early NHS ESG data into national registry frameworks to inform calibration and external validation.	
Boston Scientific Corporation	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011 – 013	001	Section 1.5 – Clinical parameters and variables (effects over time and mortality) This section could better account for the differing weight-trajectory profiles and durability of outcomes across intervention types. **Suggested addition:** We propose that the modelling guidance specify differentiated long-term weight-trajectory assumptions for pharmacological, endoscopic, and surgical interventions, informed by real-world longitudinal data. ESG, for example, typically demonstrates weight-loss durability that sits between pharmacotherapy and bariatric surgery; this should be reflected within sensitivity analysis.	Thank you for your comments, we have updated the statement accordingly.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Emerging NHS data (Rasool et al, 2025) reports sustained ~ 26% total body weight loss at 24 months following ESG, supporting the inclusion of real-world ESG trajectory data within time-effect modelling parameters.	
Boston Scientific Corporation	Obesity RCE report	1.7 Cost and healthcare resource use identification, measurement and valuation	014 – 015	020	Section 1.7 – Costs and Resource Use The cost framework is robust but would benefit from explicit consideration of capital and infrastructure costs for procedural innovations (e.g. endoscopy suite utilisation, device amortisation, and training). **Suggested addition:** We suggest expanding paragraph 1.7.1–1.7.3 to note that for interventional procedures, costs should include capital investment, device reuse parameters, organisational impact and learning-curve effects where relevant, consistent with Drummond et al. (2018).	Thank you for your comment. A new statement has been amended to capture capital investment costs for bariatric procedures. In the rationale section, the examples provided in your comment and the Drummond et al 2018 reference which was previously in the rationale for section 2 have been added. In addition, cross reference to the HealthTech and Meds Eval NICE methods manuals has been added as the latter provides guidance on costs and resource use stating: "4.4.2 Estimates of resource use should include the comparative costs or saving of the technologies and changes in infrastructure, use and maintenance. If appropriate, staff training costs should be included." "4.11.6 The costs should be disaggregated by appropriate generic organisational (for example, NHS, personal and social services, hospital or primary care) and budgetary categories (for example, drugs, staffing, consumables or capital)"
Boston Scientific Corporation	Obesity RCE report	1.7 Cost and healthcare resource use	014 – 015	020	Section 1.7 – Cost and Resource Use **Comment:** The current cost sections appropriately focus on NHS and Personal Social Services (PSS) resource use, consistent with the reference case. However, differences in recovery time	Thank you for your comment. Differences in recovery times outlined in this example are likely to be captured through the incorporation of costs associated with the interventions. These should include mean length of hospital stay and procedural complications. The inclusion of

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		identification, measurement and valuation			across intervention types may have indirect implications for patient experience, service planning, wider system efficiency, even if these are not included in base-case costs. **Proposed change:** We suggest noting that, while productivity and societal impacts fall outside the formal reference case, recovery-time differences may be explored in supplementary scenario analysis or qualitative discussion. For example, bariatric surgery typically requires several weeks of post-operative recovery, whereas ESG often enables return to usual activities within a few days. These differences may inform sensitivity analysis related to service capacity, scheduling and operational planning This preserves methodological alignment with NHS/PSS cost requirements while allowing important contextual factors to be recognised in supplementary analysis.	procedural complications has now explicitly been added to the reference case. Furthermore, quality of life should capture recovery time differences from a patient perspective. Therefore, we do not think a specific sensitivity analysis is required here.
Boston Scientific Corporation	Obesity RCE report	1.8 Equality and other considerations	031	014	Section 1.8 – Equality and Other Considerations Strong inclusion of inequality considerations, but mental-health impacts and **access equity for innovative procedures** could be more explicit. We support use of distributional cost-effectiveness analysis (DCEA) to assess how interventions like ESG may impact health inequalities across deprivation quintiles. This aligns with 1.8.1 and NICE's equity objectives.	Thank you for your comment. We have not seen evidence for unequal access to treatments and have not included it in the reference case extension.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Suggested addition: We suggest expanding the equality consideration to acknowledge potential variation in access to procedural and innovative intervention by region, socioeconomic status, gender, and ethnicity. Including this within the equality analysis would strengthen representativeness and support alignment with NHS Core20PLUS5 priorities.	
Boston Scientific Corporation	Obesity RCE report	1.8 Equality and other considerations	031	014	Section 1.8: Equality and Other Considerations The draft acknowledges inequalities in access to obesity interventions but does not consider differences in recovery time, work absence, and personal burden between surgical and minimally invasive procedures. **Proposed change:** Add that patient factors such as ability to take extended time off work, recovery requirements, and personal or caregiving responsibilities may influence access and adherence. ESG typically requires only 3 days off work compared with several weeks for bariatric surgery. Recognising this difference supports more equitable and realistic modelling of patient uptake and societal impact. Shorter recovery and lower disruption make ESG more accessible for working-age adults and those in socioeconomically deprived groups who cannot afford prolonged absence, aligning with NHS Core20PLUS5 priorities.	Thank you for your comment. This reference case extension cannot contradict NICE's methods manual, which currently only allow the inclusion of productivity gains for interventions carried out from a workforce perspective. However, we now propose that the number of extra working days per person is presented as an extra-reference case analysis alongside the CUA results. It should never be incorporated into the cost per QALY gained, as we don't have an equivalent cost-effectiveness threshold for this circumstance. We have added to the reference case extension the consideration that interventions that have less time off work might be particularly preferable for people in deprived groups.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Boston Scientific Corporation	Obesity RCE report	1.2 Intervention and comparators	019 – 020	002	Rational for section 1.2 – Intervention and Comparators The rationale on page 19 highlights inclusion of surgical comparators but does not explicitly recognise minimally invasive endoscopic bariatric interventions such as endoscopic sleeve gastroplasty (ESG). ESG has been evaluated under NICE IPG783 and is increasingly adopted across NHS sites. ESG is available in NHS hospitals, with published outcomes demonstrating its safety and effectiveness in UK practice. For example, at Darlington Memorial Hospital, patients with a mean BMI of 44.3 (range 35.3 – 57.4) achieved mean total body-weight loss (TBWL) of 17.8 %, 36 %, and 26.7 % at 6, 12, and 24 months respectively, with no major complications reported (Rasool W et al., Gut 2025; 74 [Suppl 1]: A259). These NHS results reinforce ESG's feasibility and safety profile and support its inclusion as a comparator within the reference case to reflect current and evolving NHS service configurations. **Proposed change:** To reflect current NHS practice and emerging service configurations, Section 1.2 should explicitly acknowledge minimally invasive, endoscopic bariatric interventions such as endoscopic sleeve gastroplasty (ESG), in line with NICE IPG783. ESG represents a clinically	Thank you for your comment. An edit has been made to remove the example of gastric bypass after "bariatric procedures established in NHS clinical practice" from the statement as this is not the most common procedure currently. Instead, a sentence has been added to the rationale to highlight that the sleeve gastrectomy and Roux-en-Y pass are the most common procedures in NHS currently according to the National Obesity Audit – Bariatric surgical procedure dashboard. It is considered important that any new bariatric procedure is compared to bariatric procedures established in NHS clinical practice. ESG is not currently established in NHS practice. A sentence acknowledging minimally intensive endoscopic bariatric interventions has been added to the rationale, with reference to the IPG (now HealthTech guidance 711).

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					relevant option for individuals with obesity who may not meet criteria for surgical bariatric procedures or who prefer less invasive, endoscopic approaches. Inclusion of ESG within the reference case would ensure more comprehensive representation of the continuum of weight management interventions currently offered across NHS settings. Given its distinct procedural characteristics, safety profile, and commissioning pathways, ESG should be incorporated within model structures and sensitivity analyses to enable appropriate comparison of cost-effectiveness across intervention intensities. Consideration of ESG also aligns with NICE's emphasis on capturing the evolving landscape of metabolic and obesity care, supporting consistent and forward-looking evaluation of technologies that bridge medical and surgical obesity treatment paradigms.	
Boston Scientific Corporation	Overweight and obesity management guideline - NG246	1.2 Intervention and comparators	088	-	1.18 - Surgical interventions We note that endoscopic sleeve gastroplasty (ESG) is referenced in NICE's guideline on overweight and obesity management (NG246) solely via a hyperlink to NICE IPG783, without any description or contextualisation of the intervention. This omission is notable given that ESG has been described by the NICE Chief Medical Officer, Professor Jonathan Benger, as a "welcome new option," highlighting that "surgical treatment options are in high demand	Thank you for your comment. It is outside of the scope of this development of this reference case extension to edit any part of published NICE guidance, including the guideline on overweight and obesity management.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					and not everyone wants, or is fit enough, to undergo an operation like bariatric surgery. A non-invasive procedure like endoscopic sleeve gastroplasty could be a welcome new option for some people." ESG is a minimally invasive, endoscopic procedure with growing uptake across NHS sites and private providers. It offers a valuable option for individuals living with obesity who may not meet criteria for bariatric surgery or who prefer less invasive approaches. The lack of description in NG246 risks under-recognition of ESG's role in evolving NHS obesity-care pathways. We are concerned that this omission may have contributed to oversight by implementation teams, including NICE Clinical Knowledge Summaries (CKS), which currently do not reflect ESG as a treatment option. **Proposed change:** We suggest that the Obesity Reference Case (Section 1.2) and associated NICE materials such as NG246 explicitly describe ESG, outlining its procedural characteristics and place within the spectrum of obesity interventions. This would promote consistency across NICE programmes (Guidelines, IPG, and Reference Case), support accurate modelling and commissioning clarity, and align with NICE's own innovation and service-evolution objectives.	

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
British Association for Nutrition and Lifestyle Medicine	Obesity RCE report	1.1 Population	General	General	BMI is an inadequate marker for metabolic health and hepatic steatosis as it fails to capture fat distribution and does not account for lean MASLD. Evidence supports a multi-marker approach for assessing fatty liver infiltration in obesity. Growth Differentiation Factor-15 (GDF-15) has shown strong predictive accuracy for future MASLD and MASH, reflecting systemic metabolic stress. While it has been in use at the Mayo Clinic, commercial tests are due to market in 2026. Practical indices such as the Triglyceride-Glucose (TyG) index and composite scores like the Fatty Liver Index (FLI) outperform BMI for screening purposes. Importantly, the estimated Glucose Disposal Rate (eGDR), a surrogate for insulin sensitivity, demonstrates strong inverse associations with MASLD, liver fibrosis, and cardiometabolic risk, and may outperform traditional insulin resistance markers. Homocysteine is also associated with MASLD. While definitive quantification, non-invasive imaging (MRI-PDFF or transient elastography with CAP), remains the gold standard it is also costly. NICE should consider integrating biochemical markers (e.g., GDF-15), metabolic indices (TyG, FLI), and eGDR alongside imaging for a tiered, cost-effective strategy to improve early detection and risk stratification. Refs: 1) American Diabetes Association. *Screening and Diagnosing MASLD*.	Thank you for your comment. We acknowledge the evidence provided to support the use of the listed biomarkers for metabolic health and hepatic steatosis, but it would not be practical to consider these within an economic model framework. They are not routinely reported in trials for obesity treatments (e.g. SURMOUNT-1). They are also not factors in the risk equations (e.g. QRISK) which are recommended to estimate impact of obesity-related events, so they would have to be modelled independently to these events, and it would cause the model to be unnecessarily complex. We note that these biomarkers are not listed as outcomes in the scopes for the appraisals of two treatments for MASLD. Project information | Semaglutide for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6458] | Guidance | NICE Project information | Resmetirom for treating non-alcoholic steatohepatitis and liver fibrosis [ID6529] | Guidance | NICE We will consider this comment for the upcoming MASH reference case extension that starts development in 2026.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Available from: https://professional.diabetes.org/sites/dpro/files/2025-10/hcp-screening-and-diagnosing-masld-final-10-28-25.pdf 2) Osta EG, et al. Current update on nomenclature, diagnosis, and management of MASLD. *RadioGraphics*. 2025;45(12):e240221. 3) American Association for the Study of Liver Diseases (AASLD). *Clinical Assessment and Management of MASLD*. Available from: https://www.aasld.org/practice-guidelines/clinical-assessment-and-management-metabolic-dysfunction-associated-steatotic 4) 4) Liu Y, Zhang H, Wang J et al. (2025) Association between estimated glucose disposal rate and metabolic dysfunction-associated steatotic liver disease: a cross-sectional study. *BMC Endocrine Disorders*, 25(1):1891. 5) 5) Chen X, Li M, Zhao Y et al. (2025) Estimated glucose disposal rate and MASLD-related cardiovascular risk: a prospective cohort analysis. *Journal of Global Health*, 15:04249.	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					6) Wang Y, Boutari C, Li Y et al. (2024) Proteomic profiling identifies GDF-15 as a strong predictor of MASH in UK Biobank cohort. *bioRxiv* [Preprint]. 7) Boutari C, Mantzoros CS, Wang Y et al. (2024) Circulating GDF-15 levels in MASLD: association with metabolic health and disease severity. *Cardiovascular Diabetology*, 23(1):2264. Dai Y, Zhu J, Meng D, Yu C, Li Y. Association of homocysteine level with biopsy-proven non-alcoholic fatty liver disease: a meta-analysis. J Clin Biochem Nutr. 2016 Jan;58(1):76-83. doi: 10.3164/jcbn.15-54. Epub 2015 Aug 29. PMID: 26798201; PMCID: PMC4706092.	
British Association for Nutrition and Lifestyle Medicine	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	004	1.4, 1.4.1 - Economic evaluations of interventions for obesity and other MASLD markers following AOM cessation should be assessed in both short- and longer-term. There is a need to differentiate and evaluate long term weight loss following cessation of AOM's between two scenarios: - where lifestyle interventions (wraparound care) have been provided alongside treatment, (and also potentially following end of treatment), - where AOMs have been provided without lifestyle interventions/support	Thank you for your comment. Incretin agonists are licensed to be prescribed alongside a reduced-calorie diet and increased physical activity and therefore the second scenario cannot be included in the reference case extension.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Key factors supporting weight loss maintenance following weight loss include lean mass preservation, sufficient protein intake, regular monitoring and behavioural support. Ref: Thomsen RW, Mailhac A, Løhde JB, Pottegård A. Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies. Diabetes Obes Metab. 2025 Apr;27 Suppl 2(Suppl 2):66-88. doi: 10.1111/dom.16364. Epub 2025 Apr 8. PMID: 40196933; PMCID: PMC12000858.	
British Association for Nutrition and Lifestyle Medicine	Workshop notes	Worksho p notes	003	020	DH Calorie Model is a poor tool for population health and has no place in clinical evaluations. This 2018 model relied heavily on 2011 work by Kevin Hall (formerly of NIH). In a post on X following the publication of the DH 10 Year Plan, Hall posted on 5 July 2025: *"While I'm happy that our 2011 mathematical model was used by @nesta_uk to estimate the step reduction in daily calories would be required to address obesity in the UK, I wish they had read our later studies. Unfortunately, a constant intensity intervention to reduce calorie intake typically results in exponential waning of the effect over time (not a sustained step reduction)* ***and will therefore only result in about 20% of the weight loss they predicted."***	Thank you for your comment. The DHSC Calorie Model is noted in the workshop notes for completeness as it was raised by a workshop participant. We have acknowledged that it does have some functionality for modelling weight loss and regain. We have not considered it further within our review of existing economic models, and it has not informed the development of the reference case extension, and we have made statements on weight change over time on the basis of clinical plausibility and available evidence.

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					DH Calorie Model is not fit for purpose. Refs: Hall KD, Kahan S. Maintenance of Lost Weight and Long-Term Management of Obesity. Med Clin North Am. 2018 Jan;102(1):183-197. doi: 10.1016/j.mcna.2017.08.012. PMID: 29156185; PMCID: PMC5764193.	
CEDAR, Cardiff and Vale University Health Board	Questions	Question 1	Question 1	Question 1	Overweight and obesity have wide ranging health impacts, which benefit from a comprehensive reference case extension to capture them. However, some NICE assessment programmes, for example, EVA, have very short timelines and limited evidence. This would make creating a model that fulfils the requirements of the reference case extension very challenging. A pre-existing model template populated with the risk of each health impact based on BMI, would enable the EAG to update the model with relevant evidence.	Thank you for your comment. The development of a model template is something that NICE is considering developing. This would have to go through NICE's business prioritisation process.
CEDAR, Cardiff and Vale University Health Board	Questions	Question 2	Question 2	Question 2	The use of recommended and required is helpful. It would also be helpful to summarise this in a table, or other succinct form in addition to the more descriptive text.	Thank you for your comment. We have added the terms 'recommended' and 'required' to the glossary.
CEDAR, Cardiff and Vale University Health Board	Questions	Question 3	Question 3	Question 3	For medicines and bariatric surgery, there is typically a substantial effect on BMI that occurs quickly and is longer-lasting, allowing downstream risk reduction in other health aspects.	Thank you for your comment. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. We understand the availability of high-quality evidence may be limited for such interventions.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					For digital products, the evidence base is often short term, and there may be a decline in use and impact over time. Using the intervention's measured, or estimated, short-term effects on BMI to model downstream benefits may lead to overestimation of the overall impact of the intervention.	The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.
CEDAR, Cardiff and Vale University Health Board	Questions	1.2 Intervention and comparators	Question 4	Question 4	The overall budget impact of providing digital products is likely to be less than most medicines, and the work spend on modelling should be proportionate to the decision being made.	Thank you for your comment. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.
CEDAR, Cardiff and Vale	Questions	1.4 Clinical paramete	Question 5	Question 5	It would be helpful to develop a consensus on the most appropriate tools to use. This would	Thank you for your comment.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
University Health Board		rs and variables (treatment effects and risk prediction)			avoid repetition of work and consistency, as well as ensuring that the choice was fully justified.	
CEDAR, Cardiff and Vale University Health Board	Questions	1.8 Equality and other considerations	Question 6	Question 6	Ideally there would be a role for DCEA, as obesity rates differ across socio-economic groups . However, if the uptake on interventions is uneven across these groups, together with the ability to afford private access, the disparity would be widened even more. The committee should be aware of this implication if the intervention is introduced without a targeted approach to increase uptake in more deprived groups. There will however be practical limitations in including DCEA, such as availability of evidence and the time required for additional modelling.	Thank you for your comment. We agree that it is not desirable to use DCEA to effectively increase the NICE c/e threshold. We have clarified that it's potential uses should be to prioritise subgroups for whom intervention is already below the c/e threshold. And to suggest where additional guidance recommendations to improve take-up in deprived areas might be helpful. We have also noted that there is some evidence that take-up and completion of weight management might be lower in more deprived groups and that this should be captured in DCEAs.
COMET Initiative	Obesity RCE report	1.3 Model structure and health states	General	General	We reviewed the existing COMET database entries for relevant obesity COS in terms of the core outcomes included, noting the quality of the COS development process. We extracted data on the scope, methods and participating stakeholder groups. The quality of the COS development process was assessed using the Core Outcome Set-STAndards for Development (COS-STAD) criteria(1). Core outcomes were	Thank you for your comment. The reference case extension already includes weight, cardiovascular risk and EQ-5D.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					extracted from each COS and classified according to the outcome taxonomy developed by Dodd et al(2). The search identified eight eligible published obesity COS. Five COS were developed for use in clinical trials, two COS for use in clinical practice and one for an international registry. Applicable interventions included bariatric surgery (n=3), drugs (n=1), self-management (n=1), exercise (n=1), behavioural weight management (n=1), and any intervention (n=1). We found methodological quality varied substantially across the eight obesity COS. Taking account of the COS-STAD assessments and the participant numbers, we concluded that the COS developed by Coulman et al. (2016) was methodologically sound, meeting 10* of the 12 COS-STAD criteria, and with a good number of participants with lived experience throughout the process. This COS was developed for clinical trials of metabolic and bariatric surgery interventions however, with the authors recommending general and intervention-specific outcomes(3). Across the eight COS, there are three outcomes recommended in the majority for measurement in obesity research and/or clinical practice, all of which are included in the Coulman et al. (2016) COS:	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					(i) **Weight**, with specified definitions/measures including weight change and waist circumference. (ii) **Cardiovascular disease/risk**, as defined by blood pressure, glucose levels, lipids, hepatic parameters, and renal function. (iii) **Quality of life**, with specified measurement instruments including the EQ-5D-5L and the OBESI-Q. We recommend from this review of COS that the common core outcome domains of weight, cardiovascular risk and quality of life be included in the obesity reference model case extension. The COMET database also includes multiple published and ongoing COS relating to type 2 diabetes. Some of these COS may also be relevant to the obesity reference model case extension, thus there is a need to specify the scope to identify which COS may be most appropriate. One example is the SCORE-IT COS, which established consensus on the most important outcomes for non-surgical interventions for hyperglycemia in type 2 diabetes(4). Consensus was reached on 18 core outcomes across five domains, which included outcomes relating to diabetes care, quality of life and long-term diabetes-related complications.	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					The full report is available in the COMET database: https://www.comet-initiative.org/Studies/Details/3708 **References** (1) Kirkham JJ, et al. PLoS Med. doi:10.1371/journal.pmed.1002447 (2) Dodd S, et al. J Clin Epi. doi: 10.1016/j.jclinepi.2017.12.020 (3) Coulman KD, et al. PLoS Med. doi:10.1371/journal.pmed.1002187 (4) Harman NL, et al. BMJ Open Diab Res Care. doi:10.1136/bmjdrc-2019-000700	
Eli Lilly and Company Limited	Obesity RCE report	General	General	General	Lilly welcomes the opportunity to respond to the disease-specific reference case extension: 'Management of overweight and obesity in adults' and appreciates the progressive steps taken to enhance alignment between stakeholders, to potentially streamline future submissions, reduce the volume of exchanges between companies and external assessment groups (EAG) and ultimately expedite patient access to new therapies in this indication. While acknowledging these positive developments, Lilly consider that there are several points within the reference case extension that require further clarification or refinement. Suggested amendments for these points are outlined in the following rows of this response.	Thank you for your comments; please see our responses throughout the document.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Eli Lilly and Company Limited	Obesity RCE report	General	General	General	**Planned Approach for Maintenance of the Reference Case Extension** In addition to this, the current reference case appears to closely align with EAG critique and Committee conclusions within the National Institute for Health and Care Excellence (NICE) evaluation for tirzepatide for managing overweight and obesity technology appraisal [TA1026]. However, as new evidence emerges – such as longer-term data that supports a novel approach to modelling the long-term benefit of pharmacological options – the ongoing requirement or recommendation to include certain analyses risks rendering the reference case outdated or less relevant. Given this, Lilly would welcome clarification on how the reference case will be maintained and updated over time as the evidence base evolves. In particular, Lilly request further information on the planned process and timelines for updating the reference case to ensure timely incorporation of new data and methodologies. Additionally, Lilly seek reassurance that companies will not be penalised for reasonable and transparent deviations from the reference case, especially where such deviations are justified by the latest evidence and aligned with best practices.	Thank you for your comment. We will be developing a process for maintaining reference case extensions after the obesity reference case extension has been published. We will be taking feedback from this consultation into consideration when developing this process.
Eli Lilly and Company Limited	Obesity RCE report	Question 1	General	General	**Response to Question 1: Risk of Overly Prescriptive Requirements Creating Barriers to Demonstrating Value of New Intervention to Patients and the NHS**	Thank you for your comment. We think that removing the required elements would not help NICE's objective of more consistent and higher quality models and guidance.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					While Lilly values the clarity provided by the disease-specific reference case extension, Lilly are concerned that certain elements may be overly detailed or prescriptive. This level of specificity could inadvertently constrain innovation and limit the ability to fully capture the value of interventions to patients and the National Health Service (NHS). In response to Question 1 above (How can NICE support stakeholders to ensure this reference case extension is implementable within the usual timelines of each of NICE's guidance programmes) Lilly would therefore recommend that all elements within the reference case are recommendations only rather than specific requirements. Including this flexibility will support innovation and robust health technology assessment, by allowing companies to effectively demonstrate the value of novel interventions based on the specific features and target population for each intervention. Moving away from a requirement-based reference case would also avoid unnecessary barriers to evaluation where data availability/limitations preclude all requirements from being met.	
Eli Lilly and Company Limited	Obesity RCE report	Overview	001	014 – 005	**Expectation for Submission Writing** Lilly request further clarification on the expectations for submission writing in relation to the disease-specific reference case extension. Specifically, it is currently unclear whether adherence to this reference case will be required	Thank you for your comment. NICE expects justifications for deviations from both 'required' and 'recommended' elements of the reference case extension. However, for a 'required' statement the justification would have to be particularly strong.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					to the same extent as the NICE reference case – with detailed justification needed for any deviations – or whether it is intended to serve primarily as guidance for submissions. Lilly note that the reference case extension states, "adherence to this disease-specific reference case extension should be attempted where possible," but would welcome further guidance on how this should be interpreted in practice.	
Eli Lilly and Company Limited	Obesity RCE report	1.1 Populatio n	002	005 – 006	**Subgrouping and Stratification of the Population** Overall, Lilly disagrees with the number of different stratification factors/subgroups of the population that are recommended/required in the reference case extension. Whilst some of these may be justified (e.g. Type 2 diabetes mellitus [T2DM], given the known modifying effect of this comorbidity on weight loss outcomes), Lilly are concerned that the reference case extension encourages slicing of data based on numerous patient characteristics, which could lead to small patient numbers supporting analyses and overall a weaker evidence base informing reimbursement decisions. Lilly would therefore recommend that fewer recommendations on subgrouping/stratification are included in the reference case extension to avoid encouraging analyses within small subsets of patients where uncertainty is greater, and that all stratification factors/subgroups should be recommended, rather than required.	Thank you for your comment. Please see our themed response on Population: number of subgroups.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Eli Lilly and Company Limited	Obesity RCE report	1.1 Population	002	005 – 006	**Requirement for Stratification Based on ASCVD Status** Lilly are particularly concerned with the requirement for stratification based on atherosclerotic cardiovascular disease (ASCVD) status. Whilst Lilly recognises that ASCVD is a key comorbidity in people living with overweight or obesity, Lilly strongly suggest that ASCVD status be considered a recommended, rather than a required, stratification factor during evaluation, as per other comorbidities in the disease-specific reference case extension (excluding T2DM). Beyond the fact that ASCVD is a key comorbidity in people with overweight or obesity, Lilly understand that NICE has proposed an ASCVD stratum because data for patients with established ASCVD are available for several NICE-recommended therapies for obesity, such as semaglutide (SELECT trial). However, the feasibility of making such comparisons relies on the availability of trials conducted in similarly defined ASCVD populations for each intervention. Importantly, regulatory bodies do not currently specify that separate analyses in patients with ASCVD are required for regulatory approval (whereas there are clear recommendations for conducting separate analyses/trials for patients with T2DM due to the fact that T2DM is a known treatment effect modifier for weight loss outcomes). As such, dedicated trials that enrol patients with ASCVD	Thank you for your comment. Please see our themed response on Population: ASCVD as a subgroup.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					(often cardiovascular outcomes trials [CVOTs]) typically report findings much later than registrational trials that provide the regulatory-required surrogate endpoint data. By suggesting that companies should stratify result based on ASCVD status, the reference case extension also suggests that ASCVD status is a treatment effect modifier on outcomes. However, ASCVD status is only likely to impact cardiovascular outcomes (measured in CVOTs) rather than surrogate marker outcomes recommended in the reference case (HbA1c, total cholesterol, weight, HDL and SBP). CVOT trials are inherently longer and more complex than registration weight-loss efficacy trials as they require large patient populations, extended follow-up durations, and the accumulation of sufficient cardiovascular events before analyses can be conducted. This is exemplified by studies of semaglutide, where efficacy data for obesity management (STEP-1) became available several years before results from corresponding CVOT (SELECT). Given this, it is not realistic that CVOTs will have read out at the time of appraisal. Instead, it is expected that the data available at appraisal will be surrogate endpoints (where trials are not required by regulatory bodies to stratify based on ASCVD status). Stratification by ASCVD status at submission may therefore not be feasible or valid. Whilst it may be technically possible to conduct *post hoc* stratification of populations by ASCVD	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					status in trials evaluating obesity and overweight management, this also presents challenges, including insufficient sample sizes, loss of randomisation, and lack of statistical power. These methodological limitations may compromise the reliability and interpretability of such subgroup analyses. As such, requiring ASCVD stratification risks introducing unnecessary barriers and methodological limitations to timely product evaluation. We therefore suggest that stratification requirements consider the timing and availability of robust evidence to support such analyses.	
Eli Lilly and Company Limited	Obesity RCE report	1.2 Intervention and comparators	004	015 – 006	**Intervention and Comparators** Overall, Lilly does not consider it helpful or appropriate to specify comparators within the reference case extension, as the weight management landscape is rapidly evolving, and because some options provided in UK primary care vary substantially based on geographic location. As a result, the specified comparators may become quickly outdated and may not accurately reflect the broad range of real-world clinical practice. Lilly therefore consider that it will be more appropriate and practicable for comparators to be specified as part each evaluation, as per the current NICE process.	Thank you for your comment. There were several stakeholders who responded in support of providing the minimum comparators relevant for each intervention category as per the reference case extension. These comparators are sufficiently top level that they are unlikely to become outdated, therefore it was decided to keep them in the reference case extension.
Eli Lilly and Company Limited	Obesity RCE report	1.2 Intervention and comparators	004	015 – 006	**Diet and Exercise** Lilly notes that the phrase "a reduced-calorie diet and increased physical activity" does not accurately reflect the management typically provided in UK primary care. In primary care,	Thank you for your comment. The wording has been changed as proposed to 'a healthy diet and physical activity'.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					many patients receive general advice on healthy eating and physical activity, rather than specific recommendations for calorie reduction or increased activity. Wording in the reference case extension, on page 20, lines 3–4, further supports this by acknowledging that the intensity and structure of behavioural interventions can vary significantly and recommends that different intensities and intervention types be explored in sensitivity analyses (page 20, lines 5–7 and page 20, lines 9–12). Accordingly, Lilly suggest broadening the wording to "a healthy diet and physical activity" to align with established clinical practice for patients with obesity.	
Eli Lilly and Company Limited	Obesity RCE report	1.2 Intervention and comparators	005	001	**Interpretation of 'Assessment of Bariatric Surgery'** Lilly does not consider "assessment for bariatric procedures" to be an appropriate comparator for the three subgroups detailed on page 5, lines 4–9 of the disease-specific reference case extension, as "assessment for bariatric surgery" is not a clinical intervention and, therefore, is not an appropriate comparator. The NICE health technology evaluations manual (PMG36) suggests that comparators in any evaluation should be active treatment/management options that directly deliver health outcomes,[1] such as standard medical management or bariatric surgery for those who actually receive it. Assessment, by contrast, is a triage step that is expected to form part of routine care pathways, with any associated costs–such as general	Thank you for your comment. The term assessment has been removed to clarify the intent. Further detail on the need to include incremental assessment costs for eligibility for any intervention has been added to the cost section.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					practitioner (GP) visits, investigations, or referral appointments–appropriately captured within standard diet and exercise or active medical management. The assessment itself has no intrinsic effect on weight, glycaemic control, or related complications; any impact on outcomes depends entirely on whether, and when, surgery is subsequently undertaken. Introducing comparison to "assessment for bariatric surgery" in economic models, introduces additional complexity and uncertainty, largely due to the wide variability in patient pathways following assessment. As quoted within the disease-specific reference case extension, on page 19, lines 15–17, not all those assessed for bariatric procedures will receive it. Rates of conversion are highly variable and are influenced by numerous clinical, logistical, and patient-specific factors, as supported by published data and real-world evidence.[2-4] Modelling the impact of an "assessment" rather than the actual receipt of surgery requires robust data to adequately reflect these divergent outcomes, increasing methodological complexity and the potential for uncertainty. Furthermore, using "assessment for bariatric procedures" as a comparator conflates the highly heterogeneous journeys patients undergo which leads to effect estimates and costs that are not interpretable and do not reflect real-world care for this patient population. We would therefore welcome further guidance on the rationale for selecting	

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					"assessment for bariatric procedures" as a comparator, as well as clear recommendations on the appropriate methodological approach for incorporating this comparator into economic models. This will help ensure alignment with clinical practice and modelling best practice.	
Eli Lilly and Company Limited	Obesity RCE report	1.2 Intervention and comparators	005	001	**The Role of Bariatric Surgery as a Comparator** Assuming 'assessment of bariatric surgery' has been misinterpreted and the reference case extension simply intends to specify that bariatric surgery should be a comparator, Lilly note that bariatric surgery would not constitute an appropriate comparator for adults with a BMI of 30 kg/m² or more and recent-onset T2DM, as it is not routinely offered to this population in UK clinical practice.[5-9] Clinical experts have stated that, in reality, only a minority in this group proceed to surgery, often after significant delays and through pathways that vary substantially between individuals and centres.[5-7, 9] Lilly therefore recommend that this comparator should be removed entirely for this subgroup in the reference case.	Thank you for your comment. The term assessment has been removed to clarify the intent. Further detail on the need to include incremental assessment costs has been added to the cost section. Please note that this is a recommended statement rather than a required statement and applies to the specific populations listed in the sub-bullets to reflect the NICE obesity clinical guideline. If modellers do not include bariatric procedures as a comparator for these populations, a clear justification would be required and explanation added that it has been included later in the pathway.
Eli Lilly and Company Limited	Obesity RCE report	1.5 Clinical parameters and variables (effects over time	028	003 – 005	Lilly would like to highlight a typographical error in the document: lines 3–5 are a repetition of lines 20–21 on page 27.	Thank you for your comments. We have revised it.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		and mortality)				
McMDC Ltd.	Obesity RCE report	1.1 Population	General	General	It may not be sensible to have a single reference model specification for modelling both non-T2DM and T2DM. Non-T2DM modelling will have T2DM as a possible event. But in order to avoid an overly complicated model the modelling of T2DM within a non-T2DM model will probably need to be considerably simpler than the modelling of T2DM within a T2DM model. Trial programmes may also tend to be split between non-T2DM and T2DM. Consideration should be given to having different reference model specifications for a treatment the license of which is not specific to those with T2DM (but could include T2DM patients as a small proportion of the patients recruited) and one the license of which is specific to T2DM patients. The former should be more tolerant of greater uncertainty and approximations around the cost and QALY impacts of T2DM, while the latter will need to be considerably more specific as to the complications of T2DM and possibly even specify the preferred risk functions such as those of the UKPDS. I know NICE typically wants there to be one guidance to rule them all but the split between non-T2DM modelling and T2DM modelling is so enormous in terms of events which need to be considered and how they should be modelled that I would encourage addressing them	Thank you for your comment. It is important to include statements about modelling T2DM in an obesity model. A model of obesity will be required to include T2DM progression and complications, as this is a key health state in models for this population, and people who do not have T2DM at baseline may develop it as a downstream event. Furthermore, previous economic models for obesity have captured treatment pathways and progression for T2DM, and including the statements on how to model these health states is expected to result in greater consistency across appraisals, rather than reduce it. We have aimed to be consistent where we can when making statements for modelling the T2DM and non-T2DM populations and have added T2DM-specific statements where possible and appropriate.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					separately. Should non-T2DM modelling have to consider the sequencing of treatments for T2DM in the subset of patients modelled as progressing to T2DM? This would seem difficult to avoid for T2DM modelling given that effects upon HbA1c will be central to the trial outcomes.	
McMDC Ltd.	Obesity RCE report	1.1 Population	002	001	A number of subgroups is suggested. Many of these are likely to have been prespecified within the trial protocol. To align with other NICE guidance I wonder if the subgroups should be specified on condition that they are stratification factors in the main trial, or is the reference case specifying that post hoc analyses are required? I also think that pre-diabetes status should be added to these if this will in practice be limited to trial stratification factors. I do not see the point of subgrouping by less important comorbidities such as sleep apnoea and think it unlikely that this will yield anything useful. Is the intention that for treatments that are found to be not cost effective in general they might be for those with sleep apnoea? I think pre-diabetes needs moving into 1.1.1 and greater thought given as to whether the others are likely to yield anything useful based upon previous NICE appraisals. Baseline BMI is also likely to have been prespecified within the trial protocol as a stratification factor. If the topic is a high decision risk for the NHS as seems possible for obesity drugs this will also need to consider a possible phased roll out across the NHS. There will be a	Thank you for your response. Regarding the comment on exploring modelling by BMI point and pre-diabetes as an additional population stratum, we have not incorporated these into our statements for required population strata. We acknowledge that, methodologically, these may be justified on the basis on a non-linear relationship between BMI and event outcomes or heterogeneity in the pre-diabetes group. However, we have received a large number of comments from other stakeholders in relation to the large numbers of subgroups and strata specified in the reference case extension, and that these may lead to difficulties in implementation, interpretation and evidence synthesis. Therefore, we have had to consider the balance between having sufficient population groups to capture heterogeneity in patients and cost effectiveness, and what is implementable by modellers and decision makers. This will allow for resources to be prioritised for those groups who stand to benefit the most, particularly when the introduction of a new technology will have a large budget impact, and will support stakeholders to adhere to the statements in the reference case extension.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					need for practical guidance for NHSE to be able prioritise higher risk groups. Stratification by BMI strikes me as the most obvious subgroup, with this coming before the other subgroups that are suggested. Previous NICE recommendations have also relied upon BMI subgroups. BMI subgroups seem likely to be more important than the preferred subgroups so should precede them as a consideration, also being necessary analyses rather than relegated to sensitivity analyses. Modelling should also explore BMI by BMI point and aggregate these estimates (1) within the BMI subgroups of Table 1 and (2) across the population as a whole to explore non-linearity in the modelling using an appropriate BMI distribution as guided by previous NICE appraisals; e.g. HSE data. Specifying a preferred (or even required?) source for the BMI distribution for GP administered medicines and if necessary for hospital or specialist centre administered medicines could cut through a lot of unnecessary speculation and argument.	Furthermore, it is unlikely that the required data would be publicly available for many comparators in order to model by BMI point. We have included pre-diabetes as an example of a recommended (but not required) subgroup. Please also see our themed response on Population: number of subgroups.
McMDC Ltd.	Obesity RCE report	1.1 Population	002	003	The baseline risk factors specified under 1.1.1 also appear primarily to consider the non-T2DM population. Risk factors for a T2DM licensed treatment may differ and be more specific; e.g. baseline HbA1c.	Thank you for your response. HbA1c is included in the list of risk factors to consider for allowing modelling via the risk equations.
McMDC Ltd.	Obesity RCE report	1.2 Intervention and	004	009	There is a lot of mention of comparing to diet and exercise. For tirzepatide the cost of diet and exercise (1) alone and (2) in conjunction with tirzepatide was a key model input. It is likely to	Thank you for your comment. Costing of diet and exercise from an NHS perspective is being considered as an area for research, please see the new section entitled "Real-world data

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		comparators			be so in future modelling where diet and exercise is a comparator. NHSE provided the estimates for tirzepatide. It may be desirable for this to also occur in future modelling. There may be scope for NICE to commission work on this rather than relying upon possibly opaque company commissioned estimates. While NICE has recommended treatments in primary care for obesity, companies will seek expansion to lower BMI groups so this is likely to remain a key input.	analysis to inform modelling" now included in this reference case extension.
McMDC Ltd.	Obesity RCE report	1.2 Intervention and comparators	005	001	The section on bariatric interventions, 1.2.6, seems a little glib in its consideration of T2DM. I have no knowledge of the trial base in this area but in line with my other comments I think there needs to be greater thought as to whether you need full T2DM modelling or are content with something more approximate for T2DM onset within the modelling. This will turn upon the proportion of T2DM at baseline in the relevant trials.	Thank you for your comment. The statement you are referring to reflects the populations that are eligible for assessment for bariatric surgery as outlined in the NICE guideline of overweight and obesity. It is important to include statements about modelling T2DM in an obesity model. A model of obesity will be required to include T2DM progression and complications, as this is a key health state in models for this population, and people who do not have T2DM at baseline may develop it as a downstream event. Furthermore, previous economic models for obesity have captured treatment pathways and progression for T2DM, and including the statements on how to model these health states is expected to result in greater consistency across appraisals, rather than reduce it. We have aimed to be consistent where we can when making statements for modelling the T2DM and non-T2DM populations and have

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						added T2DM-specific statements where possible and appropriate.
McMDC Ltd.	Obesity RCE report	1.2 Intervention and comparators	005	017	Section 1.2.9 is a bit glib in terms of comparing the placebo arm diet and exercise of any trial with seeing a GP once a year. This is a required analysis. Is it possible to give guidance on what the evidence base for this comparison currently or what would type of evidence would be accepted in order to demonstrate that it is feasible, and for which probable model inputs?	Thank you for your comment. This is a conservative sensitivity analysis which aims to provide an upper estimate of the ICER. It only reflects the cost difference and not the treatment difference. The rationale has been amended to explain this.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	006	008	The strictures of 1.3.1 will not be policed, the wording has a get out clause and it will have no effect upon choice of model. In its current form it is superfluous.	Thank you for your comment. The statement is broad. This acknowledges that different model forms are feasible and meaningful. It does indicate a preference for state transition models, which we think reflects the preferences of many of our stakeholders. However, it leaves room for discrete event simulations, if they are presented and reported transparently and for simpler models for comparisons where the impact might reasonably be measured over time horizons much shorter than the lifetime.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	006	014	I am unclear about tunnel health states capturing dependencies between events. In an IPS events would just be part of the vector of the current patient risk factors. Does 1.3.2 really specify anything much and is it necessary?	Thank you for your comment. We have decided to remove this statement on the basis that it relates to all models and is not specific to obesity and weight management.
McMDC Ltd.	Obesity RCE report	1.3 Model structure	006	019	1.3.4 could include pack treatment costs as requiring front loading.	Thank you for your comment. For models with annual cycles, it would not be correct to assume that a year's worth of medicines would be

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		and health states				consumed at the beginning of the year. And if monthly cycles are adopted the effect of half-cycle correction will be much smaller anyway. Therefore, we have not made this change.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	006	024	1.3.5 and 1.3.6 reflects my opinions on subgrouping as per my comments in the Population section. I think these two sections need to be better coordinated with the Population section.	Thank you for your comment. We have removed this recommendation. However, there is a reference to age-sex in the baseline risks section. It is not relevant to population as we would not want to present the results by age-sex group.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	007	003	Stroke is a quite variable phenomenon. There may be a need to present trial definitions of stroke and consideration of TIA, minor stroke and major stroke. I cannot say I am an expert on this, mark you.	Thank you for your comment. We have added some definitions. For stroke we recommend the inclusion of ischaemic stroke and unspecified stroke but exclusion of TIA, and haemorrhagic stroke.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	007	015	Doubtless intentional to permit a bit of studied ambiguity but "strata" has been introduced – possibly to avoid having to decide whether this relates to the population, subgroups within the population, prespecified trial subgroups within the population or something else. Sticking with population and subgroup might help clarify matters, with it also being made clear earlier whether subgroups will typically have to be prespecified within the trial protocol or if post hoc analyses are permitted (or indeed required?), the latter possibly being necessary for the BMI bands outlined.	Thank you for your comment. No ambiguity was intended. Strata refers to the 8 populations defined in 1.1 determined by weight, diabetes status and CVD status. These should not be combined with respect to cost-utility modelling for NICE. All the analyses required or recommended in this reference case extension are regardless of whether such an analysis was specified in the relevant trial protocols. For the trial they might be considered post-hoc but in terms of this reference case they are pre-specified.
McMDC Ltd.	Obesity RCE report	1.3 Model	007	021	Under 1.3.8 it is unclear what "progression of T2DM status" means for non-T2DM modelling.	Thank you for your comment. We have now clarified that we mean progression from

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		structure and health states			Is this just the incidence of T2DM, or incidence of T2DM and progression through T2DM treatment stages? Likewise, what does it mean for modelling of a treatment license/indication for those with T2DM?	'normoglycaemia' to 'non-diabetic hyperglycaemia' to 'diabetes'.
McMDC Ltd.	Obesity RCE report	1.3 Model structure and health states	008	007	Under 1.3.10 some of the evidence relates to hip replacements so maybe joint replacement? Presumably SAEs are included by default?	Thank you for your comment. We now include hip replacement but this needs to be a separate effect size from knee replacement, as the association between weight and hip replacement is not so great. However, given that reducing weight might not cure wearing joints, we have clarified this should only be where there is direct evidence of a treatment effect.
McMDC Ltd.	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	008	1.4.2 introduces "population stratum". It would be good to know if this differs from Population and Subgroup and try to use these terms throughout if they are all that are required.	Thank you for your comment. This has been considered and addressed in our thematic response and revised the RCE accordingly.
McMDC Ltd.	Obesity RCE report	1.4 Clinical parameters and variables (treatmen	009	011	1.4.3 is (I think) specific about modelling the incidence of T2DM. Is a subsequent section required for the modelling of "progression of T2DM status".	Thank you for your comment. This point is covered within our thematic response to related comments.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		t effects and risk prediction)				
McMDC Ltd.	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	010	004	1.4.5 suggests risk functions validated in the population specific to the stratum. Again, this may be due to the introduction of stratum as a term but is this suggesting subgroup specific risk functions? I doubt you'll get this for many of the risk functions though some will have e.g. prediabetes as a risk factor within the risk equation for developing T2DM. But if this is all it is I'm not clear what is being asked for here.	Thank you for your comment. This point is covered within our thematic response to related comments.
McMDC Ltd.	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	010	004	1.4.5 uses "relevant to an English NHS population" rather loosely. Might it be better to suggest a hierarchy of preference, with some wriggle room as to sample size/strength of relationship being relied upon; e.g. a massive US study on sleep apnoea might be preferable to an NHSE one with 120 patients? But essentially NHSE, UK, EU, …	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.
McMDC Ltd.	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk	010	013	Should 1.4.8 also suggest including trials outside the indication under consideration if necessary. It would just be for very rare events with major effects. May be less relevant to obesity where trials are likely to be large.	Thank you for this comment. The existing wording of 1.4.8 (now 1.4.10) is intended to allow the use of the most appropriate available evidence, including from related populations where necessary, particularly for rare adverse events. We therefore did not consider additional clarification to be required.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		prediction)				
McMDC Ltd.	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	003	1.5.1 I know what it means by "apply consistent assumptions on weight trajectory across all interventions to avoid bias in the relative treatment effect" but "consistent" is not the same as "the same" so I think you need to be more specific. But I also don't think that for future reviews you can preclude the company demonstrating in one arm RWE follow up studies maintenance of effect and no weight gain while on treatment. So I think there needs to be another bullet on "where there is strong evidence to suggest different long term trajectories". Perhaps this shouldn't be here under "required" but should be some allowance for it elsewhere?	Thank you for your comment. We have revised the statement accordingly.
McMDC Ltd.	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	017	1.5.7 This may be a more general point but the model should be set up to enable easy further exploration of these aspects by the EAG; e.g. the model should permit third party reviewers to easily explore (1) the trajectory of natural weight gain in both arms, (2) waning of treatment effect after cessation of treatment (3) the duration of waning of treatment effect after cessation of treatment.	Thank you for your comment, we agree with you.
McMDC Ltd.	Obesity RCE report	1.5 Clinical parameters and variables (effects	012	017	1.5.7 only considers weight gain. What should happen to the other main model inputs; e.g. pre-diabetes reversal – should this be lost? Should other continuous variables like SBP be waned in a similar manner to weight effects?	Thank you for your comments, we have updated the statement accordingly.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		over time and mortality)				
McMDC Ltd.	Obesity RCE report	1.6 Measuring and valuing health effects	014	003	1.6.2 What if neither of the second sentence is possible or available?	Thank you for your feedback. In the rationale for this section, we highlight a potential single dataset, an analysis by Luah et al. (2024), which is a regression analysis of Health Survey for England data, which estimated the association between BMI and EQ-5D-5L among the general population in England. The analysis also controlled for comorbidities such as diabetes, heart and circulatory disease, respiratory disease, musculoskeletal disease, cancer and mental health disorders. The HSE data is publicly available and could be re-analysed for provide health state utility values for an obesity model.
McMDC Ltd.	Obesity RCE report	1.7 Cost and healthcare resource use identification, measurement and valuation	015	010	1.7.6 The UKPDS provides total inpatient and total non-hospital visit costs a function of the T2DM patient comorbidities, sex and age. These are not T2DM costs but rather costs among those with T2DM. It reads as if these would be add-ons for the costs of T2DM to other costs of events within the model. This again comes back to whether there needs to be a more explicit separation of non-T2DM modelling requirements and T2DM modelling requirements.	Thank you for your comment. The statement has been amended to clarify that the UKPD provides management and complication costs for people with T2DM. Further clarification is also provided in the rationale to explain that the UKPDS costs exclude medication costs which would need to be costed separately and that UKPDS costs are for inpatient and non inpatient healthcare costs as a function of T2DM-related complication, gender and age. It is important to include statements about modelling T2DM in an obesity model. A model of obesity will be required to include T2DM progression and complications, as this is a key

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						health state in models for this population, and people who do not have T2DM at baseline may develop it as a downstream event. Furthermore, previous economic models for obesity have captured treatment pathways and progression for T2DM, and including the statements on how to model these health states is expected to result in greater consistency across appraisals, rather than reduce it.
Newcastle External Assessment Group (EAG)	Obesity RCE report	General	General	General	Concerned that there are a lot of required features of the economic model that might not be easily achievable, depending on the topic	**Thank you for your comment. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.**
Newcastle External Assessment Group (EAG)	Obesity RCE report	1.1 Population	002	003	Section 1.1.1 - Would be easier to read the different subgroups if they were tabulated in some way	Thank you for your comment, we have tabulated these subgroups to improve readability.
Newcastle External Assessment Group (EAG)	Obesity RCE report	1.4 Clinical parameters and variables	010	004	1.4.5, 1.5.1 etc - Does it mean English NHS population or NHS population in England? Concerned that the NHS population might not actually have English nationality, and this could be misinterpreted.	Thank you for your comment. This has been considered revised the RCE accordingly.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		(treatment effects and risk prediction)				
Newcastle External Assessment Group (EAG)	Obesity RCE report	1.6 Measuring and valuing health effects	014	003	1.6.2 - The last sentence is difficult to read and understand, suggest rewriting it in a simpler way	Thank you for your feedback. We have revised the wording to make the meaning clearer.
Newcastle External Assessment Group (EAG)	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	027 – 028	020 and 003	Two sentences duplicated "Many interventions show an initial weight reduction…"	Thank you for your comments. We have revised it.
NHS England	Obesity RCE report	Overview	001	009 – 010	The scope of the guideline is not clear enough. Please specify that this reference case extension applies to evaluations of technologies where the primary indication/reason for treatment is management of overweight/obesity. To distinguish from, for example, semaglutide's indication for reducing the risk of cardiovascular disease events in people with established cardiovascular disease and overweight/obesity.	Thank you for your comment. Obesity treatments are used to both reduce weight and reduce or improve weight-related comorbidities. The aim is for the best outcomes for patients. Obesity treatments are included in this reference case extension regardless of whether the primary indication is the treatment of a comorbidity, such as cardiovascular disease or type 2 diabetes.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						If the indication does not include overweight or obese at least in part. Then the reference case need not apply.
NHS England	Obesity RCE report	1.1 Population	002	003	1.1.1 - The reference case by disease adds welcomed specificity to cost-effectiveness appraisals where patients or participants present with comorbidities that directly affect clinical outcomes (1.1.1). However, Recommendation 1.1.1 requires stratifying the population into groups defined by 3 characteristics (overweight or obese; T2DM; ASCVD). This could lead to imprecise estimates of treatment effect within a stratum (due to small samples), and/or estimates of treatment effect that are at risk of bias (if these were not randomisation stratification factors in the trial). Potentially, this could lead to spurious conclusions about greater clinical and cost-effectiveness in one stratum over another. Doubtless NICE committees would consider this, but NICE normally steers companies away from post hoc subgroups so it seems odd to mandate it here.	Thank you for your comment. Please see our themed response on Population: number of subgroups.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
NHS England	Obesity RCE report	1.1 Population	003	004	Table 1: BMI categories by ethnic group - Analysis of population by BMI provides important detail, where the ranges of BMI and corresponding classification (particularly for obesity class I–III), cover a wide cohort of patients with obesity, as well as the likelihood of clinical comorbidities depending on obesity class. This often has a direct impact on clinical effectiveness, therefore is instrumental for recommendations.	Thank you for your comment and support for the statement.
NHS England	Obesity RCE report	1.1 Population	003	004	Table 1: BMI categories by ethnic group - "Other Asian" appears to be missing from the ethnicities requiring a lowered BMI threshold in Table 1 (BMI categories by ethnic group). NICE guidance on BMI classification here.	Thank you for your comment. We have now included "other Asian" in the table.
NHS England	Obesity RCE report	1.1 Population	003	008	1.1.4 - Sub-stratification analyses according to comorbidities could be required rather than recommended (1.1.4). Consider whether a comorbidity risk score e.g. CCI might be included where subjects have multiple comorbidities For MASLD, and where mentioned throughout, consideration should be given as to need for pathway development, which is not yet established everywhere	Thank you for your comment. We have kept the statement as 'recommended' rather than 'required'. This is because we have received a large number of comments from other stakeholders in relation to the large numbers of subgroups and strata specified in the reference case extension, and that these may lead to difficulties in implementation, interpretation and evidence synthesis. Therefore, we have had to consider the balance between having sufficient population groups to capture heterogeneity in patients and cost effectiveness, and what is implementable by modellers and decision makers. However, to emphasize its importance, we have removed the statement to consider it as part of a sensitivity

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						analysis, so that it is now considered as part of the base case analysis. We understand that CCI is used more in research and question how implementable it would be if recommended in practice. We note that a lot of the conditions in the CCI score are not specific to obesity (such as AIDS, hemiplegia) and some obesity-related conditions are not captured (MASLD, OSA). We will be developing a MASLD reference case extension later this year, and we will consider pathway development for managing this condition as part of that process.
NHS England	Obesity RCE report	1.1 Population	004	003	1.1.6 - Regression analysis by BMI/BMI category and type/number of comorbidities could be required rather than recommended (1.1.6). This would support clinical cohorting for evidence-based NHS delivery and prioritisation of high-cost drugs.	Thank you for this comment. We have deleted the statement as it was unclear. The section on clinical parameters now contains more information about estimating treatment effects.
NHS England	Obesity RCE report	1.2 Intervention and comparators	005	001	1.2.6 - Bariatric surgery as a comparator should be required rather than recommended, given that this is still the gold standard and has the best long term outcomes and evidence based. The justification for why the reference case has this as only recommended on p19 is unclear – further clarity would be appreciated as to why bariatric surgery is not considered as required.	Thank you for your comment. This was a recommended statement to reflect the fact that the bariatric procedure recommendations in the NICE obesity guideline are a combination of weaker 'consider' recommendations and stronger 'offer' recommendations, due to uncertainty in the clinical and cost-effectiveness. In addition, these are recommendations for assessment for bariatric procedures. Following assessment only a proportion will go onto receive surgery. Overall, therefore in clinical practice not all people in those subpopulations will receive or are eligible for bariatric surgery.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
NHS England	Obesity RCE report	1.2 Intervention and comparators	005	010	1.2.7 - If an intervention or comparator is indicated alongside a behavioural intervention, consider this being captured in the model for the duration of the treatment specified (1.2.7). Where interventions do not last for the entire treatment period, this should be reflected in the model to ensure that the behavioural intervention is not over- or under-represented. For example, the Behavioural Support for Obesity Prescribing Programme is a one-off intervention lasting for 9 months.	Thank you for your comment. The wording of that statement has been changed to state that the duration of the concomitant behavioural intervention should reflect current NHS practice. Sensitivity analyses exploring the intensity and duration are required.
NHS England	Obesity RCE report	1.2 Intervention and comparators	005	014	1.2.8 - Consider capturing different intensities of behavioural intervention as a required rather than recommended element of analysis (1.2.8). In long-term cost-effectiveness analyses – for instance, pharmacotherapy combined with intensive behavioural intervention – the intensity of the intervention is likely to influence the degree of long-term weight change. This has further implications for policy guidance on best practice alongside pharmacotherapy and other interventions to determine the recommended level of intervention required.	Thank you for your comment. Please note that these sensitivity analyses only change costs not treatment effects due to lack of data, therefore they are associated with limitations. As this reference case extension needs to apply to all obesity interventions, changing this to a required statement may make it unachievable for certain interventions.
NHS England	Obesity RCE report	1.2 Intervention and comparators	005	017	1.2.9 - Clarification may be needed on 1.2.9, given variation in local service provision. How is "minimal intervention of GP advice" defined? Does this refer to advice given at appointment, which is variable and difficult to measure, or to a low-level Tier 2 intervention such as those offered by Better Health/NHS Digital Weight Management Programme?	Thank you for your comment. This is a conservative sensitivity analysis which aims to provide an upper estimate of the ICER. It only reflects the cost difference and not the treatment difference. The rationale has been amended to explain this.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
NHS England	Obesity RCE report	1.2 Intervention and comparators	005	017	1.2.9 - Please clarify that recommendation 1.2.9 refers only to modelling a *comparator* arm of no pharmacological treatment and GP advice once a year. Intervention arms should not model minimal behavioural support in conjunction with a medicine, I doubt it would comply with GLP-1 licences.	Thank you for your comment. The statement has been amended to clarify this applies only to the behavioural intervention alone comparator.
NHS England	Obesity RCE report	1.3 Model structure and health states	006	016	1.3.3 - Although referenced in rationale notes below, consideration needs to be given here to account for likelihood of continuation/discontinuation of intervention, and risk of weight regain, return or exacerbation of comorbidities, where possible	Thank you for your comment. We think that the term 'outcomes' is broad enough to cover all of those things.
NHS England	Obesity RCE report	1.3 Model structure and health states	006	024	1.3.5 - Sex should be included (specifically sex, rather than gender, to account for differential biological risk)	Thank you for your comment. We have changed 'gender' to 'sex' in the glossary to be clear.
NHS England	Obesity RCE report	1.3 Model structure and health states	007	015	1.3.7 - To note, for the purposes of the funding variation for tirzepatide heart failure within the ASCVD domain was included. This may introduce an inconsistency if then excluded form future modelling.	Thank you for your comment. As heart failure has multiple aetiologies, we have only included chronic heart failure after MI within the ASCVD cohort. Likewise, we have only included post-MI chronic heart failure as an outcome.
NHS England	Obesity RCE report	1.3 Model structure and health states	008	007	1.3.10, 1.3.11 - (notwithstanding the explanation that comes later in the doc) Why is obstructive sleep apnoea the only condition included in cost and QALY losses of health events (1.3.10)? Other conditions such as hypertension or dyslipidaemia also contribute to reduced quality of life and increased healthcare utilisation.	Thank you for your comment. This reference case extension sets minimum standards. It will always be theoretically possible to create more sophisticated models. We have

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					Consider other weight-related comorbidities for inclusion. Further clarity would be helpful on the below: • Why the 5 specific cancers have been selected? • Why hip replacement hasn't been included? • Which CKD stages are to be included, or all? Is the intention to include all stages of MASLD?	applied some proportionality to the selection of health states. Hypertension and dyslipidaemia can be controlled for most patients with cheap generic medicines. Sleep apnoea is more expensive to treat. The 5 specific cancers have been included in other NICE models, specifically the guideline update that used the PrimeTime model. We have now included hip replacement. We have distinguished CKD stage G5 from stages G1-G4 as treatment is considerably greater. But both are included. Modelling of MASLD is a developing area and this is partly why the statement is for a sensitivity analysis. For models that focus on people with MASLD at baseline – it might be necessary to model multiple health states – see forthcoming reference case extension on MASH. For other models a single health state might be sufficient.
NHS England	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects	009	002	1.4 - Good to see the sections on "Clinical parameters and variables (treatment effects and risk prediction)" (1.4) and "Clinical parameters and variables (effects over time and mortality)" (1.5). In particular, the option to explore partial waning of treatment effect on weight loss over time.	Thank you for your comment.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		and risk prediction)				
NHS England	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	003	1.5.1 - A fourth option to explore effects over time could be considered: "exploring majority waning of treatment effect", in addition to only "*partial* waning of treatment effect" on weight loss over time.	Thank you for the comment. Majority waning is included in the partial waning.
NHS England	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	019	1.5.2 - Treatment duration and discontinuation are essential to incorporate in the obesity/overweight cohort (1.5.2). Current options include discontinuation due to adverse effects, inefficacy, or remission, but there is no option for patient self-directed discontinuation. Consider including in analyses. Also need to consider adverse effects of interventions	Thank you for your comment. We have included discontinuation due to patient self-directed in the updated rationale. The intention has already included adverse effects of interventions and adverse effects due to other reasons.
NHS England	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	003	1.5.4 - Case for discontinuation of behavioural support/continuation is not yet established. This will need reviewed when the evidence emerges.	Thank you for your comment. Model should reflect the current provision including concomitant behaviour.
NHS England	Obesity RCE report	1.5 Clinical	012	007	1.5.5 - Factoring discontinuation into the relative treatment effect is crucial to consider effect of	Thank you for your comment. We will keep this as recommended rather than required. This is

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		parameters and variables (effects over time and mortality)			treatment over time and relative clinical utility and efficacy (1.5.3). Due to the effects of discontinuation on weight regain, consider amending modelling treatment discontinuation over time (1.5.5) as a required rather than recommended factor in analyses. Cost-effectiveness analysis cannot fully reflect patient treatment without incorporating weight regain following discontinuation, particularly where real-world evidence demonstrates a significant effect. We propose this should be required, not recommended for the above reasons.	because the likelihood of obtaining RWE evidence may be low due to feasibility challenges. Even though it is not mandatory, company still need to provide a justification to ensure transparency and robustness.
NHS England	Obesity RCE report	1.3 Model structure and health states	007 – 008	021	1.3.8 - Consider an additional factor in analysis to be included in 1.3.8: change in comorbidity status (beyond T2DM, ASCVD or prediabetes) where data is available.	Thank you for your comment. For other risk factors such as hypertension, we are capturing treatment effects. If you are suggesting that we should also incorporate change in these factors over time, then we don't believe this is practical or necessary. And it hasn't been captured in existing models for obesity management.
NHS England	Obesity RCE report	1.7 Cost and healthcare resource use identification, measurement and valuation	015	010	1.7.6 - Are there other examples that could be given, eg for Obstructive Sleep Apnoea?	Thank you for your comment. As part of the development of this reference case extension a systematic review of cost sources was not undertaken, this should be conducted by modellers. Diabetes was highlighted because it is a complex, influential parameters and a UK costing source (UKPDS) use is established.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
NHS England	Obesity RCE report	1.2 Intervention and comparators	019	027 – 029	Analysis of other weight interventions in the preceding 12 months should be undertaken (whether obtained on NHS or privately) due to good evidence of weight re-gain on discontinuing GLP-1RA and how this might impact on data validity. This is partially addressed in p.27, lines 20-24.	Thank you for your comment. The model should include the baseline weight of the cohort at the start of the intervention. The impact of prior treatment on weight would not be captured. Capturing the impact of use of GLP1-RAs in the preceding 12 months would be challenging as RCTs are likely to exclude those who have received such medicines in their trials and real-world evidence would not capture this due to private prescriptions making up most prescriptions in the UK. However, over the time horizon of the model, any discontinuation of treatment and subsequent weight gain would be captured.
NHS England	Obesity RCE report	1.2 Intervention and comparators	020	010	Does it need to be a GP, or could it be a HCP within primary care/community settings?	Thank you for your comment. This was meant to be just an example of minimal support for people with obesity. However, it could be another health care professional.
NHS England	Obesity RCE report	1.2 Intervention and comparators	020	018 – 022	This does not cover the use of SGLT-2 inhibitors in heart failure. Also, if semaglutide is used for treatment in diabetes vs weight loss vs cardiovascular disease prevention – how would this be accounted for in modelling?	Thank you for your comment. The use of SGLT-2 inhibitors for T2DM was included in the rationale as it is one of the determining factors for the modelled population. Similarly mention of background treatments for ASCVD were included. Heart failure is considered as a clinically relevant subgroup or event. The reference case extension does not give details for all clinically relevant subgroups or events occurring in the model.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						As an individual cannot receive an incretin agonist twice, costs would need to be adjusted to avoid double counting of semaglutide.
NHS England	Obesity RCE report	1.3 Model structure and health states	024	008 – 019	Propose to include endometrial cancer in which there is evidence that weight loss can improve histological staging and disease progression.	Thank you for your comment. Endometrial cancer is already included in the reference case extension under the term womb cancer..
NHS England	Obesity RCE report	1.6 Measuring and valuing health effects	013 – 014	025	1.6 - Good to see EQ-5D included (1.6.1).	Thank you for your feedback and support for this statement.
NHS England	Obesity RCE report	1.8 Equality and other considerations	015 – 016	019	1.8 - For equality and other considerations (1.8), consider factoring analysis by level of deprivation as required rather than recommended.	Thank you for your comment. We have left this as 'recommended', since data for such analysis is currently limited. Also, the NICE manuals currently prohibit EAGs from conducting distributional cost-effectiveness analysis.
NHS England	Obesity RCE report	1.8 Equality and other considerations	015 – 016	025	1.8.2 - Organ transplants but also dialysis which has significant costs associated with it.	Thank you for your comment. We had no intention of being inclusive in this statement because the examples are numerous, as you point out elsewhere. In the rationale we have noted that these items can have significant associated costs to the NHS as well as extra benefits to patients.
NHS England	Obesity RCE report	1.8 Equality and other	032	014 – 016	There are many other examples which could be considered here, noting variation from ICB level down to individual clinicians.	Thank you for your comment. We had no intention of being inclusive in this statement

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		considerations			For example, access to surgical interventions such as hip and knee replacements are restricted to those under a certain BMI threshold, AF ablation is not recommended for those with BMI > 40. It is not uncommon for patients to be referred to Specialist Weight Management Services for help to lose weight prior to consideration or being placed on a waiting list for a surgical procedure (despite NICE guidance).	because the examples are numerous, as you point out. However, we don't think hip and knee surgery are suitable examples here, as the reference case extension includes explicit modelling of these procedures.
NHS England	Questions	Question 2	Question 2	Question 2	Yes, the distinction between 'required' and 'recommended' is helpful.	Thank you for your comment.
NHS Greater Manchester ICB	Obesity RCE report	General	General	General	The document provides a comprehensive framework, and standardised approach for assessment of clinical and cost-effectiveness, which is welcomed. It will support consistency in decision-making, and alignment of access to treatments for overweight and obesity across subgroups and clinical pathways. Reporting of outcomes, adverse effects and cost-effectiveness by cohorts and subgroups including levels of risk is key to informed decision making.	Thank you for your comment and support for the reference case extension.
NHS Greater Manchester ICB	Questions	Question 2	Question 2	Question 2	**Is the distinction between 'required' and 'recommended' helpful in bridging the gap between enhancing consistency and allowing flexibility?** This seems like a reasonable and balanced approach. Including a clear and justifiable rationale for not providing recommended information will be important to minimise the risk of bias in submissions and to encourage primary	Thank you for your comment.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					research (where feasible) rather than an over-reliance on modelling/extrapolations.	
NHS Greater Manchester ICB	Questions	Question 3	Question 3	Question 3	**Should HealthTech (such as digital products) have the same requirements as for medicines and bariatric surgery?** It is important that HealthTech evaluations follow the same core principles and that there is consistency in the assessment of outcomes and cost-effectiveness. There should be some specific requirements for HealthTech to ensure inclusivity and user acceptability by protected characteristics.	Thank you for your comment. We note your view, and that of other stakeholders who have suggested that there should be more flexibility for digital technologies where benefits, costs and risks might all be quite small. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention. This reference case extension is for obesity only and provisions related to equality of access still apply (as for all assessments).
NHS Greater Manchester ICB	Questions	1.8 Equality and other considerations	Question 6	Question 6	**The role of distributional cost-effectiveness analysis (DCEA) is referred to in the NICE manuals but is not currently included within the NICE reference case. Do you think there is a role for DCEA to inform decision-making specifically around the management of**	Thank you for your comment. It is not desirable to use DCEA to effectively increase the NICE c/e threshold because of the opportunity cost. We have clarified that it's potential uses should be to prioritise subgroups for whom intervention is already below the c/e threshold. And to

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					obesity (see 1.8.1)? When decision-making/access to an intervention is based on DCEA, there is a trend towards more widespread approval, linked to postcode/deprivation quintile. This does not necessarily equate to uptake in the intended population or a reduction in inequities. To maximise the health benefit of available budgets, a population health approach with criteria linked to evidence of outcomes and prioritised based on the greatest clinical need is required. Specifically for obesity, linking decision-making to DCEA/deprivation would undermine the significant amount of work that has been undertaken to prioritise and phase access to tirzepatide/weight loss services based on clinical need. Consideration of the DCEA is key for implementation. An understanding of the differential impacts of an intervention on social groups/levels of deprivation allows approaches to be tailored with a focus on reducing health inequalities.	suggest where additional statements to improve take-up in deprived areas might be helpful.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
NHS Greater Manchester ICB	Questions	Question 7	Question 7	Question 7	**Can you suggest some research recommendations that would support further development of this reference case extension?** Research on longer term outcomes, side-effects and approach to discontinuation of treatment and weight regain is needed to validate predictive models. It is important that, where real-world evidence is used, steps are taken to ensure its independence. Further research into the role of weight loss in cardiovascular health vs any specific therapy effects is needed – particularly in those under 45yrs with lower immediate risk but potentially high lifetime risk	Thank you for your comment. We have developed a list of priority research recommendations and have considered your suggestions.
Novo Nordisk Ltd	Obesity RCE report	1.1 Population	General	General	Overall, Novo Nordisk welcomes the principle of extending the obesity reference case. However, it is critical that the subgroups by type of comorbidity reflect the qualifying comorbidities for access to pharmacotherapy. We urge alignment and clarity between NICE and NHS England to support real-world implementation - particularly ensuring that NHS England's risk stratification and prioritisation of qualifying comorbidities for access to obesity pharmacotherapy is consistent with this reference case extension. Subgroups should be considered on a case by case basis dependent	Thank you for your comments. NICE is committed to working with NHS England to enable equitable access to new technologies, and statements in this reference case extension should ensure that all technologies are considered in a consistent manner and that NHS resources can be prioritised for those who need them most. The reference case extension also highlights in its statements that only strata relevant to the intervention's target population need be modelled, and where the target population is more specific than a single

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					on the value proposition of the medicine being appraised and the evidence base that supports it.	stratum, only that specific population should be modelled. Please also see the themed comment on Population: number of subgroups.
Novo Nordisk Ltd	Obesity RCE report	1.2 Intervention and comparators	General	General	The requirement to include discontinuation of behavioural interventions (1.2.9) combined with requirement to consider behavioural interventions as a comparator (1.2.2) means that models are required to consider costs and outcomes for patients discontinuing behavioural interventions. All modern drug therapy trials have been conducted in addition to behavioural interventions: it would not be ethical to allow patients in a clinical trial to discontinue their diet and exercise advice. This requirement cannot be met with robust data by any modern drug therapy.	Thank you for your comment. The sensitivity analysis in what was previously labelled as "1.2.9" is for the behavioural intervention alone comparator, not for behavioural interventions as an adjunct to medicine, clarification has been added now. This is a conservative sensitivity analysis which aims to provide an upper estimate of the ICER. It only reflects the cost difference and not the treatment difference. The rationale has been amended to explain this.
Novo Nordisk Ltd	Obesity RCE report	1.3 Model structure and health states	General	General	The appropriate choice of model states and populations should reflect the strength of the underlying evidence; however, the evidence changes over time. New data is emerging from large scale studies that may justify a different segmentation of the population and provide additional evidence of important outcomes benefits that should be included as additional states. The reference case as written does not allow the models to evolve when the evidence changes. It would be more robust to reword these sections to state that:	Thank you for your comment. We have added a statement to use specific criteria to select health states and events in the model, similar to your suggestion. We have made it clearer that the outcomes we suggest are those that we believe to be evidence-based but we are clearer about where direct evidence is required. We will be developing a process for maintaining reference case extensions after the obesity reference case extension has been published, which can be used to maintain all future reference case extensions. This will include

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					• health states and subgroups in the model should be included on the basis of clear criteria • the list of states and subgroups presented reflects application of these criteria to the evidence reviewed at the time of writing changes to the list presented would need to be justified using the same criteria, with explanation of what new evidence or analysis caused the model authors to arrive at a different list	updating reference case extensions when new evidence and knowledge come to light or new comparators are approved. This will include comparators being available in other populations.
Novo Nordisk Ltd	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	General	General	The reference case recommends that the effectiveness of interventions be modelled by using surrogate outcomes (1.4.1) and linking these to final outcomes using risk prediction tools (1.4.4); directly measured outcomes should be used to validate or calibrate findings (1.4.7). Evidence based medicine (EBM) principles however gives higher weight to directly observed evidence than to modelling based on surrogate markers. The reference case reverses this approach. It would be more consistent with established EBM to state that the effectiveness of interventions should ideally be based on direct evidence of outcomes from clinical trials when this is available. However, it should be stressed that it is also appropriate to assess the effectiveness of obesity interventions by using surrogate outcomes when direct evidence is not	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					available. Examples where surrogate marker modelling is appropriate include: • extrapolating over longer time horizons than studied in trials • extrapolating to populations or subgroups where direct evidence is limited • interventions where direct evidence does not exist and only surrogate markers are available. The economic modelling of obesity should remain flexible and be tailored to the value proposition of the medicine and evidence availability at the time of appraisal. This is in line with other modelling recommendations such as the those included in NICE's HTA Lab report for modelling metabolic dysfunction-associated steatohepatitis. Separately, 1.3.11 identifies some states that should be included as sensitivity analyses "if there is direct evidence of a treatment effect". This contradicts EBM principles. If there is direct evidence of a treatment effect this should be included in our base case assumptions, insofar as the effect is robustly demonstrated and important to the decision at hand.	
Novo Nordisk Ltd	Obesity RCE report	1.4 Clinical paramete	General	General	The reference case recommends or requires presentation of data specific to individual subpopulations (1.4.2 - efficacy; 1.5.7 - weight	Thank you for your comment. This has addressed in our thematic response.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		rs and variables (treatment effects and risk prediction)			gain over time). Accurate and robust data does not exist to separately inform each of the large number of strata identified in 1.1.1, 1.1.2 and 1.1.3 so this recommendation cannot be met. It would be preferable to require that evidence used be the most appropriate for each stratum considered and recommend a structured explanation of the process used to identify potential data, evaluate appropriateness and to select the preferred source.	
Novo Nordisk Ltd	Questions	Question 1	Question 1	Question 1	Novo Nordisk would propose opportunities for early engagement to discuss the technology that has been topic selected and ensure the reference case extension aligns with the value proposition of the medicine.	Thank you for your comment. We acknowledge that early engagement would be helpful.
Novo Nordisk Ltd	Questions	Question 2	Question 2	Question 2	Yes, this is helpful to distinguish between 'required' and 'recommended' in bridging the gap between enhancing consistency and allowing flexibility. However, it is important to ensure that the reference case is flexible to ensure it can accurately capture evolving therapy areas it serves.	Thank you for your comment. We agree that the reference case extension needs to be flexible enough to ensure it can accurately capture evolving therapy and might need to be updated regularly.
Novo Nordisk Ltd	Questions	Question 3	Question 3	Question 3	While ideally HealthTech should have the same requirements, given the differences in evidence requirements at a regulatory level, this may not always be feasible. Therefore, early engagement with NICE should be sought to ensure that there is sufficient flexibility to capture the evolving therapy areas they serve.	Thank you for your comment. We have not developed a separate reference case extension for digital technologies. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. We understand the availability of high-quality evidence may be limited for such interventions., The overview section provides clarification of when this

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
						reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.
Novo Nordisk Ltd	Questions	1.2 Intervention and comparators	Question 4	Question 4	Given the delayed implementation of obesity medicines in the NHS and what may be considered standard of care based on BMI class and associated comorbidities, it may present operational challenges specifying appropriate comparators that may change at the point of the draft scope being issued for future appraisals.	Thank you for your comment. There were several stakeholders who responded in support of providing the minimum comparators relevant for each intervention category as per the reference case extension. These comparators are sufficiently top level that they are unlikely to become outdated, therefore it was decided to keep them in the reference case extension.
Novo Nordisk Ltd	Questions	1.4 Clinical parameters and variables (treatment effects and risk prediction)	Question 5	Question 5	Yes, this would be helpful as important long-term outcomes may not necessarily be captured during the trials, which inform marketing authorisation. In the absence of clinical trial data, risk equations which inform CV risk, T2D progression etc are helpful to include e.g. UKPDS, QRISK3, Framingham.	Thank you for your comment.
Novo Nordisk Ltd	Questions	Question 7	Question 7	Question 7	The draft reference case excludes the adolescent patient population. There is a paucity	Thank you for your comment. Children and adolescents are outside of the scope of this

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					of robust age-specific evidence for modelling. However, this is a high unmet need and underserviced patient population, and we would welcome consideration of alternative measures for assessment, via, for example, a medicines policy for children approach applies, or to follow the Scottish Medicines Consortium (SMC) where they do not seek a submission for paediatric indications, where as of January 2020 that, "*From January 2020, abbreviated submissions for paediatric licence extensions will no longer be requested. We will update ADTCs when paediatric licence extensions are granted and highlight advice for the corresponding indication in adults, however no SMC advice statement will be issued*." Source: Minor process changes introduced	reference case extension and therefore we cannot make research recommendations. However, we have passed on your comments to the NICE surveillance team.
PenTAG, University of Exeter	HE literature review	HE literature review	009	012 – 013	Decision analytic model is not a model structure. It's either state transition, DES or something else	Thank you for this comment. We have ensured that the specific model structure is specified for each study.
PenTAG, University of Exeter	Obesity RCE report	General	General	General	It is important to note that the current required standard is not feasible for de novo construction of a model by an EAG for the Healthtech programme in the timescales available for either an EVA or a routine use assessment. It would require the construction of an open-source model all EAGs could use outside of an assessment / appraisal that could then be adapted for specific use cases.	Thank you for your comment. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					It is much more feasible for companies within the STA process as companies start model construction ~ 2 years prior to an appraisal. For companies coming to submission shortly after this is published there may still be issues so should leeway should be allowed for provision of additional analyses after initial submission.	about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention. NICE are conducting bespoke data analyses to provide baseline risks for use by EAGs and other stakeholders to support the building of a reference case model. NICE will consider whether the development of a reference model in this area is a priority.
PenTAG, University of Exeter	Obesity RCE report	General	General	General	The benefits of having a reference case model (in addition to greater standardisation) might include greater efficiency and increased overall quality. These benefits will only be realised if there is one reference case model used by manufacturers / EAGs which is shared, QC'd and available for adaptation. This sort of initiative is best when there is an academic group at the heart of the model build initiative and manufacturers and patient and clinical groups contribute to the development (including contributing registry data for the analysis). Think something like project HERCULES. NICE has a golden opportunity to kick start this sort of initiative so it is a shame not to see this in here.	Thank you for your comment. Following the publication of our position statement on the use of reference models, this is an area that we will continue to explore and monitor opportunities for collaboration. We will be considering developing an obesity reference model in the future when determining the priorities for our workstream.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
PenTAG, University of Exeter	Obesity RCE report	1.1 Population	002	020	Subgrouping should be used to reflect differences in either the baseline risk of events or the treatment effect of the intervention as well as to capture existing thresholds for surgical interventions and medications	Thank you for your comment. We have included the impact on treatment effect in the statement.
PenTAG, University of Exeter	Obesity RCE report	1.1 Population	004	005	It would be good to provide some guidance on implementation of regression analysis to avoid inappropriate analysis e.g. use of mean of covariates rather than corrected group prognosis methods when applying in the economic model. See the Ghali paper	Thank you for this comment. We have deleted the statement as it was unclear. The section on clinical parameters now contains more information about estimating treatment effects. However, we have decided not to go into the specifics of statistical analysis.
PenTAG, University of Exeter	Obesity RCE report	1.1 Population	004	007 – 008	Odd formatting on link to population section	Thank you for your comment. We have amended the formatting on this link.
PenTAG, University of Exeter	Obesity RCE report	1.2 Intervention and comparators	004	010 – 014	Suggest add phrase along the lines of 'attempts should be made to be as inclusive as possible and exclusions adequately justified' (perhaps even add a statement to that effect as the first clause in section 1.2 – I'd recommend this for all NICE docs on descriptions of interventions and comparators)	Thank you for your comment. The first statement about including all potentially relevant comparators that are established practice is "required", and so by definition is considered the best approach. In addition, the NICE position statement on Disease-specific reference case extensions states that any deviations should be explained and justified and agreed by committees and NICE's quality assurance processes. adequately justified. (see ECD18). Therefore, to avoid duplication we will not add additional information here. The overview does also provide more detail and cross references to the position statement and a glossary which defines the strength of statements.
PenTAG, University of Exeter	Obesity RCE report	1.2 Intervention and	004	018 – 028	Surely all interventions should be compared with all other options if the objective is to find the most cost-effective treatment for obesity? The	Thank you for your comment. In this section we have listed the minimum comparators which are considered current NHS practice for each type

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		comparators			definition of the population will limit the options (eg surgery wouldn't be compared with diet and exercise as it is not a first line option)	of intervention. Additional comparators can be included if they are relevant to the population.
PenTAG, University of Exeter	Obesity RCE report	1.2 Intervention and comparators	006	001	This sensitivity analysis is only required if the trial does not match what would be expected in practice	Thank you for your comment. The statement has been edited to reflect this.
PenTAG, University of Exeter	Obesity RCE report	1.3 Model structure and health states	006	014	Tunnel states may also be required in an individual-level state transition model depending on method of implementation (could also use additional states or trackers). Some more information on how to capture multiple events / time dependency for cohort vs individual-level models would be helpful.	Thank you for your comment. However, we have decided to remove this statement on the basis that it relates to all models and is not specific to obesity and weight management.
PenTAG, University of Exeter	Obesity RCE report	1.3 Model structure and health states	006	016	Suggest state the appropriate time horizon is that sufficient to capture all differences in cost and outcomes.	Thank you for your comment. We agree and since those words reflect the wording of the manuals, we have deleted the statement altogether.
PenTAG, University of Exeter	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	004 – 007	It is not clear to me why use of surrogate outcomes with calibration would be preferred if we are in a lucky situation where good quality hard outcomes data are available	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
PenTAG, University of Exeter	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	024	Discontinuation due to remission may need handling differently in terms of implication for treatment effect than other types of discontinuation	Thank you for your comments. We agree with you. Discontinuation occurs due to several reasons including remission. However, it may be difficult to incorporate this data into economic modelling, given that discontinuation rates are not often recorded in databases or reported in the literature in this way.
PenTAG, University of Exeter	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	021 & 025	Would prefer to recommend structured expert elicitation over clinical expert opinion	Thank you for your comments. We will keep it as "clinical expert opinion" to be consistent with our manual. In the situation where there is a lack of robust quantitative evidence, both informal and formal expert opinion can be used.
PenTAG, University of Exeter	Obesity RCE report	1.6 Measuring and valuing health effects	013	015	Do you mean age and sex?	Thank you for this comment. Yes, this has now been edited.
PenTAG, University of Exeter	Obesity RCE report	1.6 Measuring and valuing health effects	014	013	Would suggest providing some guidance on duration of utility decrements for AEs as this is often poorly done in manufacturer models.	Thank you for your feedback. We have provided further clarity in the rationale on how AE disutilities should be estimated.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
PenTAG, University of Exeter	Obesity RCE report	1.7 Cost and healthcare resource use identification, measurement and valuation	015	010	Guidance is provided here on potential sources of costing data but similar guidance is not provided for potential sources for risk equations etc… which would have been extremely helpful. Could signpost to page 26 in the earlier text / would be good to cover the equations discussed in Appendix B more thoroughly	Thank you for your comment. This point is covered within our thematic response 5 "risk equations" to related comments.
PenTAG, University of Exeter	Obesity RCE report	1.8 Equality and other considerations	015	025	Surprised not to see anything on use of societal perspective in scenario analysis given government focus on treatment to increase work	Thank you for your comment. This reference case extension cannot contradict NICE's methods manual, which currently only allow the inclusion of productivity gains for interventions carried out from a workforce perspective.
PenTAG, University of Exeter	Obesity RCE report	1.3 Model structure and health states	021	010 – 018	This is mixing up tracking (either via tunnels in a state transition structure, additional states or trackers) or use of a DES structure with individual level simulation as a method to better capture heterogeneity.	Thank you for this comment. We think the paragraph is reasonably clear and we were not referring to DES structures.
PenTAG, University of Exeter	Obesity RCE report	1.3 Model structure and health states	022	011	Should say relevance not relevant	Thank you for your comment. This has been corrected.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
PenTAG, University of Exeter	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	026	General	When talking about surrogacy it would be good to match the discussion to be clear on what counts as level 1 vs level 2 surrogacy and where prior obesity modelling falls on that scale	Thank you for your comment. This has been considered and addressed in our thematic response and revised the reference case extension accordingly.
PenTAG, University of Exeter	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	028	003 – 005	This is repeating text from page 27	Thank you for your comments. We have revised it.
PenTAG, University of Exeter	Obesity RCE report	1.6 Measuring and valuing health effects	030	003	This is not in line with DSU guidance which suggests a multiplicative approach as the preference (it is unlikely surely that the effects are independent)	Thank you for your feedback. We have provided further clarification around the application of multiplicative and additive utility values in the rationale, and have cited the relevant DSU guidance.
PenTAG, University of Exeter	Obesity RCE report	1.8 Equality and other considerations	031	028	Important to point out that current threshold does not account for use of the DCEA approach. DCEA helps quantify how an intervention's costs and benefits are distributed among different population groups with respect to equity. If inequalities are reduced or equity gains are demonstrated by an intervention, NICE guidance	Thank you for your comment. We agree that it is not desirable to use DCEA to effectively increase the NICE c/e threshold. We have clarified that it's other uses should be to prioritise subgroups for whom intervention is already below the c/e threshold. And to suggest where additional guidance recommendations to

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					indicates that this may justify accepting interventions with ICERs above the usual threshold but no guidance has been given on how this should work and use of DCEA only to increase the applicable threshold for a TA (and not reduce it where an intervention increases inequality) would lead to overall increasing of the NICE c/e threshold which is not sustainable / desired.	improve take-up in deprived areas might be helpful.
Perspectum	Obesity RCE report	1.3 Model structure and health states	024	001	MASLD has been listed as a health event recommended for inclusion in the sensitivity analysis due to the emerging or partial evidence of a treatment effect. Perspectum asks that NICE update this section to include the ongoing Single Technology Assessment titled: *Semaglutide for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis.* The inclusion of this guideline may provide more weight and justification to this important health event in health modelling.	Thank you. We have added this forthcoming NICE guidance to the text.
Perspectum	Questions	Question 2	Question 2	Question 2	*Is the distinction between 'required' and 'recommended' helpful in bridging the gap between enhancing consistency and allowing flexibility?* The distinction between required and recommended is helpful, however we feel that there should be clarity regarding the weighting given to assumptions that have a higher degree of uncertainty or classified as 'recommended'	Thank you for your comment. We have added the terms 'recommended' and 'required' to the glossary to improve this clarity.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Perspectum	Questions	1.2 Intervention and comparators	Question 4	Question 4	*Is it helpful to specify appropriate comparators or will this present operational challenges in applying the reference case extension? (see 1.2.2-1.2.6)?* This is helpful, however there needs to be an allowance for differing clinical care across the NHS, especially since there may be healthcare inequity among this patient population.	Thank you for your comment. The reference case extension allows for multiple comparators, those listed are a minimum requirement.
Perspectum	Questions	1.4 Clinical parameters and variables (treatment effects and risk prediction)	Question 5	Question 5	*Would it be helpful to recommend specific risk tools / equations in this reference case extension, if yes, which ones and why (see 1.4)?* This would be helpful, to ensure consistent modelling techniques, assessments and comparisons for different interventions and comparators. Risk equations included in the UKPDS study may be a good starting point.	Thank you for your comment.
Perspectum	Questions	1.8 Equality and other considerations	Question 6	Question 6	*The role of distributional cost-effectiveness analysis (DCEA) is referred to in the NICE manuals but is not currently included within the NICE reference case. Do you think there is a role for DCEA to inform decision-making specifically around the management of obesity (see 1.8.1)?* There is a role for DCEA to inform decision making, especially in the case of obesity whereby there is a higher incidence within areas	Thank you for your comment. We have clarified that DCEA's potential uses should be to prioritise subgroups for whom intervention is already below the c/e threshold. And to suggest where additional guidance recommendations to improve take-up in deprived areas might be helpful, such as CDCs. We have also noted that there is some evidence that take-up and completion of weight management might be lower in more deprived

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					of greater socioeconomic deprivation. This is even more relevant and applicable with the introduction of Community Diagnostic Centres across England that were created with the goal of providing care in the community and away from hospitals. These CDC's provide greater access and improve healthcare equity to those in areas of socioeconomic deprivation.	groups and that this should be captured in DCEAs.
Perspectum	Questions	Question 7	Question 7	Question 7	*Can you suggest some research recommendations that would support further development of this reference case extension?* Given that children and young people are not included in the current scope, this patient population should be considered an area for research recommendation for further development.	Thank you for your comment. Children and adolescents are outside of the scope of this reference case extension and therefore we cannot make research recommendations. However, we have passed on your comments to the NICE surveillance team.
Pfizer Ltd	Obesity RCE report	General	General	General	Given the uncertainties and evolving evidence base, we recommend that the reference case extension be subject to ongoing review and periodic updates as new long-term outcomes, and real-world data become available. In addition, it would be helpful for the guidance to specify how frequently these reviews and updates will occur, and to clarify the ownership and responsibility for maintaining and updating the reference case models over time.	Thank you for your comment. We will be developing a process for maintaining reference case extensions after the obesity reference case extension has been published. We will be taking feedback from this consultation into consideration when developing this process.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Pfizer Ltd	Obesity RCE report	General	General	General	The extensive sensitivity and scenario analyses recommended in the reference case extension, in addition to those in the existing NICE reference case, will significantly increase resource requirements. We suggest a list of sensitivity analyses be agreed upon during the scoping phase, to ensure feasibility.	Thank you for your comment. We have reduced the number of analyses slightly since the original draft. We will consider your suggestion as we develop processes for implementing this reference case extension.
Pfizer Ltd	Obesity RCE report	1.1 Population	002	008 – 015	The requirement for detailed stratification (e.g., by T2DM, ASCVD, BMI, and ethnicity) may not be feasible in practice due to limited data availability, especially for rare combinations. We recommend the guidance clarify whether subgroup analyses are mandatory in such cases, or if pragmatic approaches (such as combining strata) are acceptable when data are sparse.	Thank you for your comment. Please see our themed response on Population: number of subgroups.
Pfizer Ltd	Obesity RCE report	1.1 Population	002	024 – 025	We support the recommendation to subgroup by BMI obesity class (I-III), as there is evidence for differences in QoL for patients with obesity class I to III. We suggest this stratification be considered in the base case (ref 1, ref 2), not just in sensitivity analyses, where data allows.	Thank you for your comment and support for the statement. We have reconsidered our statement, and this is now this is now part of the base case..
Pfizer Ltd	Obesity RCE report	1.3 Model structure and health states	007	013	The requirement for line of treatment 'if applicable' in the strata containing people without T2DM and ASCVD is unclear, we suggest clarifying which disease is this referring to (i.e., overweight/obesity, TD2M or ASCVD).	Thank you for your comment. We have edited this to be clear it refers to treatment of overweight/obesity.
Pfizer Ltd	Obesity RCE report	1.4 Clinical parameters and	009	004 – 019	• Please provide clarity on the definition of surrogate outcomes within the proposed guidance. Our understanding is that surrogate outcomes refer to variables	Thank you for your feedback. Both your comments regarding surrogate outcomes and the use of risk equations have been considered and addressed in our thematic response and

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		variables (treatment effects and risk prediction)			incorporated into risk equations to estimate the incidence of T2DM and ASCVD, for example, and not be modelled directly as outcomes. • The recommendation for surrogate outcomes to be specific to the population stratum may result in increased uncertainty if the relationship between surrogates and outcomes is not well established in these groups. Therefore, when data for a particular stratum are insufficient, the guidance should encourage validating surrogate-outcome relationships in the most relevant available population. The guidance provides a recommended minimum list of surrogate outcomes for predicting changes in the incidence of ASCVD and T2DM. However, the surrogate outcomes used are limited to those available within the chosen risk equation. For example, the QDiabetes tool, used in TA875 for semaglutide in overweight and obesity, does not include eGFR to predict T2DM, even though eGFR is recommended as a surrogate outcome in the reference case extension. We suggest the guidance acknowledge that surrogate outcomes used, are dependent on the chosen risk equation.	revised the reference case extension accordingly. The list of risk factors is presented as a statement, where relevant and consistent with the inputs required by the selected risk prediction tool or risk equation.
Pfizer Ltd	Obesity RCE report	1.3 Model structure	022	011 – 014	We welcome the recommendation that the model is aligned to relevant core outcome sets (COS), it is timely and opportune. We believe	Thank you for your comment. Where there are several core outcomes set, we recommend that the quality of the COS development process can

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		and health states			that all parties would benefit from further guidance and clarification around how these COS will be interpreted in terms of quality, relevance and content (i.e. Both "what" outcome and "how" it is measured and the specific population/ setting in question). We note the existence of multiple COS already in this disease space, and while there are high levels of congruence between them, there are also differences, particularly with regard to PRO measures for HRQoL.	be assessed using the Core Outcome Set-STAndards for Development (COS-STAD) criteria(1). A recent report in the COMET database (2) concluded that the COS developed by Coulman et al. (2016) was methodologically sound, meeting 10* of the 12 COS-STAD criteria, and with a good number of participants with lived experience throughout the process. (1) Kirkham JJ, et al. PLoS Med. doi:10.1371/journal.pmed.1002447 (2) https://www.comet-initiative.org/Studies/Details/3708 (3) Coulman KD, et al. PLoS Med. doi:10.1371/journal.pmed.1002187
Pfizer Ltd	Obesity RCE report	1.8 Equality and other considerations	032	011 – 013	The requirement that impact on mental health should be captured by the EQ-5D if measured during the trials may not provide a full or thorough understanding of the full value of the interventions, or the impact on mental health. This is largely due to the complex nature of mental impact (i.e. often a non-linear recovery) and the known issues in capturing mental health on the EQ-5D, which has been explored within dermatology. This section of the guidance is somewhat in contrast to the recommendation that important outcomes such as mental health are not recommended for quantitative modelling and should be addressed qualitatively. We	Thank you for your comment. We agree that mental health should be modelled but do not agree that the EQ-5D is inadequate

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					suggest that other methods/ measures of quantifying mental health should be considered with regard to economic modelling, and clarity provided on how qualitative information will be incorporated into committee decision-making, and whether alternative utility generating measures such as SF-6D can be referenced as a viable alternative. Finally, we note that the literature presents specific measures for obesity such as the BODY-Q, QOLOS, and IWQOL, these measure capture a range of domains (including some not captured on the EQ-5D) that are deemed important to patient HRQoL and lived experience, we welcome further direction from NICE regarding the use of and interpretation of these measures.	for capturing improvements in the area of obesity. The methods suggested for calculating utility by weight and comorbidity should adequately account for mental health. Similarly, we have proposed that mental health costs also be captured within health state costs if possible. This means that mental health has now been lifted out of the qualitative section.
PrescQIPP CIC	Obesity RCE report	General	General	General	We strongly support the development and implementation of a disease specific reference case extension for the management of overweight and obesity in adults and would support extrapolation of this approach to other disease areas. The document provides a comprehensive framework for standardising clinical and economic evaluations of obesity interventions.	Thank you for your comment and support for the reference case extension.
PrescQIPP CIC	Questions	Question 2	Question 2	Question 2	Is the distinction between 'required' and 'recommended' helpful in bridging the gap between enhancing consistency and allowing flexibility? We agree that this is a reasonable approach to ensure that essential information is captured whilst allowing some flexibility. However, the	Thank you for your comment. We have added the terms 'recommended' and 'required' to the glossary.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					rationale for the decision to use 'recommended' versus 'required' needs to be clear and consistent, to ensure that essential information is not missed.	
PrescQIPP CIC	Questions	Question 3	Question 3	Question 3	Should HealthTech (such as digital products) have the same requirements as for medicines and bariatric surgery? We believe that HealthTech evaluations should be subject to the same core principles, but have their own reference case extension that ensures consistency in evaluation, but where the requirements are appropriate for non-medical and non-surgical interventions.	Thank you for your comment. We have not developed a separate reference case extension for digital technologies. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. We understand the availability of high-quality evidence may be limited for such interventions. The overview section provides clarification of when this reference case extension is applicable or may be applicable. A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention.
PrescQIPP CIC	Questions	1.2 Intervention and comparators	Question 4	Question 4	Is it helpful to specify appropriate comparators or will this present operational challenges in applying the reference case extension? (see 1.2.2-1.2.6)? Ideally specific comparators should be specified; however, we recognise there may be operational challenges for both NICE and Pharma should	Thank you for your comment. There were several stakeholders who responded in support of providing the minimum comparators relevant for each intervention category as per the reference case extension. These comparators are sufficiently top level that they are unlikely to

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					the appropriate comparators change in clinical practice. If appropriate comparators are specified these will need to be updated in the reference case if clinical practice changes.	become outdated, therefore it was decided to keep them in the reference case extension.
Roche Products Ltd	Obesity RCE report	1.1 Population	004	003	Please clarify what "Regression analysis by BMI or BMI category and type or number of comorbidities to be undertaken where possible." means and provide additional details on what it is intended to inform. Is it the treatment effect or something else?	Thank you. We agree that this was unclear and it has now been removed.
Roche Products Ltd	Obesity RCE report	1.2 Intervention and comparators	005	001	Bariatric surgery is normally already modelled as an event within risk equations. Overall, its role in obesity management in clinical practice is limited (i.e. 0.1% eligible patients go onto receive it, as noted in past assessments) [TA875]. See Comment 20.	Thank you for your comment. This is a recommended statement rather than a required statement and applies to the specific populations listed in the sub-bullets to reflect the NICE obesity clinical guideline. If modellers do not include bariatric procedures as a comparator to medicines for these populations, a clear justification would be required and explanation added that it has been included later in the pathway.
Roche Products Ltd	Obesity RCE report	1.2 Intervention and comparators	005	014	Please clarify if, when exploring different intensities of behavioural intervention, this should be done for all treatment arms.	Thank you for your comment. As stated in the rationale, this should be done separately for the concomitant and standalone behavioural interventions.
Roche Products Ltd	Obesity RCE report	1.3 Model structure and health states	006	019	Please clarify what "Transformations […] should generally be half-cycle corrected." means or if there is a typo.	Thank you for your comment. We agree that this was not well expressed. We have revised this to say 'time in health state' instead of 'transformations'.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Roche Products Ltd	Obesity RCE report	1.3 Model structure and health states	007	021 – 026	Should progression of CKD be considered for inclusion as a movement between health states?	Thank you for your comment. We have added progression of CKD to the list.
Roche Products Ltd	Obesity RCE report	1.3 Model structure and health states	008	006	Should the same wording in parenthesis also be added here, as in line 7? i.e. (unless there is direct evidence for the intervention)	Thank you for your comment. We prefer to keep the distinction, as there is evidence that some interventions, such as surgery, can reverse diabetes in some patients but we are not aware of evidence for any intervention reversing ASCVD.
Roche Products Ltd	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	008	For the weight loss change and surrogate outcome measures: similar considerations as mentioned in Comment 18.	Thank you for your comment. This point is covered within our thematic response to related comments.
Roche Products Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	011	007	Please clarify if the 'rate of weight change over time' refers to baseline weight, or something else? Please also clarify the recommended way of modelling treatment effect waning (i.e. via baseline weight trajectory or weight regain)	Thank you for your comments. "Rate of chang over time" refers to the initial weight. We prefer modelling treatment effect waning through percentage change from baseline in the body weight and apply hazard ratio accordingly.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Roche Products Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	007	For the rate of discontinuation over time: See Comment 18 Please also clarify if "baseline discontinuation rate" only refers to discontinuation rate on behavioural intervention when used alone	Thank you for your comment. The baseline discontinuation rate refers to the discontinuation observed under the behavioural intervention when behavioural change is used as the comparator. However, if high-quality RWE is available, the baseline discontinuation could refer to the rate observed in the comparator arm (not limited to behavioural intervention) and trial-derived treatment effect could be applied to that estimate.
Roche Products Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	015	Please clarify if (and how) the impact of dose changes over time is expected to affect the intervention resource use beyond just drug costs	Thank you for your comment. We have updated the statement and rationale accordingly.
Roche Products Ltd	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	015	See Comment 18 The use of threshold analyses to determine optimal treatment duration may risk promoting inconsistencies with decisions taken in past recommendations (for example in TA1026 tirzepatide NICE guidance has no limitations in treatment duration for the population that is recommended for reimbursement).	This statement will only apply to the new therapy entering the market. If the new treatment shows a treatment waning effect, it is less likely to be cost-effective indefinitely. Identifying an optimal treatment duration is therefore essential to reflect the true clinical benefits.
Roche Products Ltd	Obesity RCE report	1.5 Clinical parameters and	012	017	For the rate of weight regain overtime: See Comment 18	Thank you for your comment. We think you are suggesting that capturing weight regain will be difficult for digital health technologies. We have added to the reference case extension that the

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		variables (effects over time and mortality)				RCE should be applied proportionately for digital technologies.
Roche Products Ltd	Obesity RCE report	1.6 Measuring and valuing health effects	013	019	Please clarify how BMI history (assumed at baseline) is expected to be accounted for, particularly in the context of recurrences / remissions with anti-obesity medications – which may make accurate determination of BMI history challenging, both in RCTs and in the real-world. Please provide guidance on how its impact on outcomes and mortality is expected to be explored in sensitivity analyses, especially when using risk equations without taking BMI history into account.	Thank you for your comment. We agree that this is challenging. Hence why it is suggested as a sensitivity analysis and not in the base case analysis.
Roche Products Ltd	Obesity RCE report	1.3 Model structure and health states	007 – 008	015 & 024	There is an inconsistency between these two sections in the deck. In the first case, it is recommended that the impact of CKD and HF is captured as an explicit health state in the model, whereas in the second one it is recommended to do so (and only for CKD, for unclear reasons) only if there is evidence of a treatment effect and only as part of sensitivity analyses. Please clarify.	Thank you for your comment. We have revised the reference case extension, such that CKD is recommended in the base case analysis for all strata.
Roche Products Ltd	Obesity RCE report	1.7 Cost and healthcare resource use identificat	030	025 – 029	Please clarify if adjustment in costs is only expected to be conducted in case of overlap between background comorbidity and acute event costs (e.g. subtract one-off costs) or also to be conducted in case of overlap between background costs of different comorbidities (and if so how).	Thank you for your comment. This statement is intended for all overlaps. The wording in the rationale has been edited to clarify this.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		ion, measure ment and valuation				
Roche Products Ltd	Questions	Question 1	Question 1	Question 1	There are a high number of items that are listed as "required", and should be considered as "recommended", particularly with respect to the subgrouping requests. At the time of NICE submission, it is highly likely that there will be significant unresolvable data gaps against the elements that have been listed as required within this disease specific reference case. Realistically, the ability to explore these fully for all required subgroups will be extremely challenging to undertake in the timeframe from pivotal trial read out to TA submission development. Furthermore, many of the requested subgroup analyses are unlikely to be informative as some of the strata determining factors (such as ASCVD) are not effect modifiers of weight loss activity. Finally, the prevalence of some of the required subgroups in typical cardiovascular, renal and metabolic (CVRM) RCTs are very small and so are likely to be statistically insignificant. Overall, the restriction on what elements are "required" can limit how manufacturers can demonstrate a technology's value proposition, and more flexibility should be given to also limit the uncertainty in data gaps at the point of	Thank you for your comment. We have tried to reduce the number of required elements where we can. The population of this reference case extension is very large indeed. We note that the number of subgroups is large. However, clinicians and commissioners have made it clear that being able to focus obesity treatments on the individuals or subgroups for whom it is most beneficial and cost-effective is of critical importance. The importance of subgrouping will be that the absolute baseline risk of an event could vary even where there is no significant heterogeneity in the relative treatment effect.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					technology appraisal, i.e. listing more or all elements as recommended.	
Roche Products Ltd	Questions	Question 2	Question 2	Question 2	Whilst the distinction is clear, there are too many elements marked as "required" to allow for any flexibility or future ability to demonstrate value propositions for technologies. Realistically, manufacturers will not be able to address all listed required elements reliably due to limitations in the available evidence base. A key example is within the population strata: the prevalence of overweight patients in typical CVRM trials tends to be smallest across the BMI categories (ranging from ~6-17% in trials enrolling patients with and without T2DM, respectively). Similarly, the prevalence of ASCVD in typical CVRM trials tends to also be quite low (~5-10%). It is also worth noting that the ASCVD definition generally used in CVRM trials tends to be broader than the CVD conditions needed for the modelling (i.e. stroke and MI), thus restricting the effective subgroup size with differing background risks even further. This will realistically make any baseline data for such subgroup categories highly unreliable at the time of first submission. Additionally, it is highly unlikely that outcome data for comparators will be available for these subgroups, as the listed cut-offs are not typically used as stratification factors and/or are not reported in publications, resulting in subgroup specific ITCs being infeasible. In the case that	Thank you for your comment. An obesity treatment that is cost-effective in a population living with obesity is likely to be less cost-effective in a population living with overweight. Therefore, pooling these strata together for the purposes of economic evaluation is not appropriate. If you consider there to be enough evidence for the overweight stratum then what you could do is apply a suitable baseline risk to a suitable hazard ratio. The baseline risk would be best from a real-world population. The pooled hazard ratio from the trial can be used in the population living with overweight, unless there is statistical or other evidence of heterogeneity in the relative effect size between the strata. If there is heterogeneity then stratum-specific hazard ratios could be used. A similar approach can be taken for the ASCVD stratum. We have made this approach clearer in the revised reference case extension. In the final version of the reference case extension, we have clarified that our definition of ASCVD is broader than stroke and MI. In the case of the availability of data for a comparator treatment for a specific stratum then

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					the outcome evidence was available, the small sample size to inform subgroup ITCs will create high uncertainty within the results. It would be helpful to understand whether in such circumstances (i.e. infeasibility to conduct reliable subgroup analyses for a certain population in a given stratum [e.g. ASCVD]) it would be acceptable to still present analyses for the overall stratum (e.g. obese without T2DM, irrespective of ASCVD status), or would it still be required to generate evidence for the specific population strata for which this is feasible (e.g. patients without ASCVD). Overall, the requested approach risks promoting inconsistencies with past NICE recommendations with the same disease area (e.g. tirzepatide in patients with BMI 35+ and +1 comorbidity, irrespective of ASCVD status). The required elements in the population strata of this reference case, could result in unresolvable high uncertainty in the cost-effectiveness estimates of a new technology in patients with ASCVD, which may potentially result in a decision to exclude these patients from reimbursement, even though the new technology provides the same pivotal trial evidence as tirzepatide. In principle. this issue may apply to most of the other subgroup and sensitivity analyses flagged as "recommended". The sample size of CVRM studies does not allow for all strata analyses (listed as required and recommended) to be	it might be plausible to apply the overall relative treatment effect from the comparator's trial, especially if you have found no statistical heterogeneity between strata in your own trial. This approach of combining baseline risks from real world evidence with hazard ratios from trials far from adding unresolvable uncertainty, serves to both provide estimates for cost-effectiveness in different strata and subgroups, at the same time as highlighting where evidence is lacking.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					reliably conducted, creating high uncertainty and misinforming Committee decision making.	
Roche Products Ltd	Questions	Question 3	Question 3	Question 3	No, requirements should be more flexible to reflect that the evidence base for digital health technologies will be substantially different from that for drugs. Evidence standards framework for digital health technologies (ECD7) should be sufficient for DHT evaluations.	Thank you for your comment. It was decided that the principles of this reference case extension are relevant to all interventions, including digital health technologies. We understand the availability of high-quality evidence may be limited for such interventions. The overview section provides clarification of when the reference case extension is applicable - either wholly or in part (i.e. individual RCE statements). A sentence has been added to clarify that the applicability would be decided at scoping. In addition to the existing sentence about adherence, further information is provided about how deviations should be managed. Therefore, there is opportunity at scoping and throughout development to assess the applicability and level of adherence required for a given intervention. .
Roche Products Ltd	Questions	1.2 Intervention and comparators	Question 4	Question 4	Similar to the draft scope for TAs, it can be helpful however this should not be restrictive (i.e. comparators listed as required) given the dynamic and rapidly changing treatment landscape within this disease area. The comparators could also vary for each of the population strata listed, and market shares/usage in the real world can change (an example at Comment 2). Furthermore, this could result in the reference case extension requiring	Thank you for your comment. There were several stakeholders who responded in support of providing the minimum comparators relevant for each intervention category as per the reference case extension. These comparators are sufficiently top level that they are unlikely to become outdated, therefore it was decided to keep them in the reference case extension.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					additional updates/becoming out of date if comparators are no longer used or not included due to new developments.	
Roche Products Ltd	Questions	1.4 Clinical parameters and variables (treatment effects and risk prediction)	Question 5	Question 5	Yes, this would allow manufacturers to only focus their efforts in implementing risk equations that will be taken into consideration or preferred, while leaving out those considered not very informative/reliable or suboptimal. Having a minimum required set would help standardisation.	Thank you for your comment.
Roche Products Ltd	Questions	1.8 Equality and other considerations	Question 6	Question 6	A DCEA would likely show that anti-obesity medications are most cost-effective in high BMI populations, which is expected. As BMI is negatively correlated with socio-economic status, the consideration of this analysis could support the reduction of inequality in this patient population/disease area.	Thank you for your comment. We have retained a statement DCEA be conducted.
Roche Products Ltd	Questions	Question 7	Question 7	Question 7	To ensure the reference case extension is futured proofed, can specific recommendations and/or guidelines for the acceptance of new or additional risk tools/equations be provided to help with the development and implementation of these for future technology appraisals.	Thank you for your comment. We have made a research recommendation for risk tools in this area.
SCHARR-TAG	Obesity RCE report	General	General	General	The principles in the Reference Case extension are welcome, although as I do not have extensive knowledge of modelling in this disease area I cannot comment on specifics. However, I would recommend some words to the effect that in extraordinary circumstances it may be	Thank you for your comment. We will be developing a process for maintaining reference case extensions after the obesity reference case extension has been published, and we acknowledge its importance. We will be taking feedback from this consultation into

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
					permissible to not follow the guidance when new insights/ data have occurred since publication, but any deviations need to be explicitly justified, and an analysis following the recommendations would also need to be performed. This would not constrain the analysis when there is a genuine reason to prefer an alternative approach.	consideration when developing this process. This will include acknowledging new insights or data have occurred since publication, when deviations can occur and how to update the reference case extension.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	General	General	General	While the reference case is comprehensive, its length and presentation may present challenges for practical use. It may be helpful to supplement the document with a concise checklist or summary guide to facilitate user engagement and implementation.	Thank you for your comment. We will consider developing a checklist as part of ongoing implementation activities. Each of NICE's guidance producing programmes are developing processes to facilitate the use of reference case extensions.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	General	General	General	It is not clear how the reference case extension aligns with the existing general reference case (PMG36 Table 4.1). Some elements appear to just repeat what is already in the reference case and are thus redundant. For instance 1.2.1 says "The model should include all potentially relevant comparators that are established practice in the NHS for managing weight and reducing weight-related comorbidities …" which is dealt with in the existing reference case via the scope. It would be useful to organise the disease-specific extensions in line with Table 4.1 in PMG36.	Thank you for your comment. We recognise that some comments are similar to those already set out in the existing general reference case, but there are some instances where it should be reinforced in the obesity context, and that they are generally proceeded by further statements that provide further context and detail. We considered creating a summary table similar to that for the general reference case, but we found that there were too many statements and they contained too much detail to be adequately summarised in this way. However, we shall be considering the presentation of the reference case extension report as part of ongoing implementation activities.

Disease-specific reference case extension: Management of overweight and obesity in adults

Stakeholder comments table
05/11/2025 – 03/12/2025

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	General	General	General	It wasn't immediately clear to us whether the reference case extension is intended to add extra elements to the reference case (e.g. preferred model structure), give examples of how the current reference case should be interpreted for a given disease, or a mixture of the two.	Thank you for your comment. It should be interpreted as a mixture of the two: model structure is an example of where it adds extra elements to the reference case, while areas such as comparators demonstrate how it should be interpreted within the context of obesity management.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	General	General	General	The structure and content of the document is very specific to overweight and obesity, which makes it difficult to imagine how this could be replicated across other disease areas in a way that would promote consistency across all NICE decisions. We suggest that a core set of extensions are identified (for instance, 1.1.2 could essentially be applied to any disease "Further subgrouping should be undertaken to reflect differences in baseline risk of events and to capture existing thresholds for surgical interventions and medications")	Thank you for your comment. While the content is naturally going to be specific to obesity, as the intended purpose of the document is to provide disease-specific statements for modelling, we have updated the structure and headings of the document so that it can be applied within other disease areas.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	General	General	General	It may be easier to read and apply the reference case if the requirements and recommendations were summarised, with the exposition and background text dealt with elsewhere. This would help the EAG when reviewing to quickly identify which elements need to be checked against the reference case, particularly if the topic is in a disease area they are not familiar with.	Thank you for your comment. We have already captured the exposition and background text in the rationales, while keeping pertinent information within the statement so that it can be understood from reading without having to refer to other parts of the document for context. However, we shall be considering the presentation of the reference case extension report as part of ongoing implementation activities.
University of Liverpool -	Obesity RCE report	Overview	001	001	We were confused as to whether this extension is intended to be disease-specific (i.e. treating	Thank you for your comment. Obesity treatments are used to both reduce weight and

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
Liverpool Reviews and Implementation Group (LRiG)					overweight and obesity, so reducing BMI is the primary outcome since that defines overweight and obesity) or population specific (i.e. people with overweight and obesity but the drug may be treating a condition in this population that isn't necessarily directly associated with BMI).	reduce or improve weight-related comorbidities. The aim is for the best outcomes for patients. Obesity treatments are included in this reference case extension regardless of whether the primary indication is the treatment of a comorbidity, such as cardiovascular disease or type 2 diabetes. If the indication does not include overweight or obese at least in part. Then the reference case need not apply.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	1.2 Intervention and comparators	004	010	It is unclear how this is any different to the standard reference case, that is, comparators should be those listed in the NICE scope.	Thank you for your comment. In this reference case extension, unlike in the standard reference case which says comparators are listed in the scope, minimum comparators required for each type of intervention are listed.
University of Liverpool - Liverpool Reviews and Implementation Group (LRiG)	Obesity RCE report	1.4 Clinical parameters and variables (treatment effects and risk prediction)	009	004	This requirement implies that the effect of the treatment is primarily via BMI changes. However, this is not necessarily the case. For instance, in the SELECT trial, which was measuring the effect of semaglutide treatment on MACE for patients with established CVD, there was a reported effect that was not directly associated with weight loss hence a risk algorithm based on BMI would not capture this effect.	Thank you for your comment. This point is covered within our thematic response to related comments.
York Health Economics Consortium (YHEC)	Obesity RCE report	1.3 Model structure and	006	024	Section 1.3.5 Model structure and health states: If an evaluation is being made for a whole population, different age and gender cohorts should be modelled separately. This is because	Thank you for your comment. We think that our statement is sufficiently strong on this.

Stakeholder	Document	Section	Page No	Line No	Comments	Developer's response
		health states			the long-term outcomes will be non-linear, and using an 'average' starting age may produce highly misleading results.	
York Health Economics Consortium (YHEC)	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	017	Section 1.5.7 Clinical parameters and variables: Consider the inclusion of additional scenario to estimate the impact of rapid fluctuation of weight (rather than just using absolute weight as a proxy).	Thank you for your comment. However, it would be difficult to capture this impact at the population level,
York Health Economics Consortium (YHEC)	Obesity RCE report	1.5 Clinical parameters and variables (effects over time and mortality)	012	017	Section 1.5.7 Clinical parameters and variables: Consider the inclusion of additional scenario where weight returns to a higher level than the underlying trend.	Thank you for your comment. Based on the evidence from the study weight regain after cessation of medication for weight management: systematic review and meta-analysis (West et al., 2026), we have updated the statement and suggest Including scenario where weight returns to pre-treatment weight quicker instead.
York Health Economics Consortium (YHEC)	Questions	1.8 Equality and other considerations	Question 6	Question 6	Section 1.8.1 Equality and other considerations: If equity is important to NICE, then DCEA should be considered.	Thank you for your comment. Equity and efficiency are both important to NICE and our stakeholders.

Thematic responses to stakeholder comments

This section provides thematic responses to some of the consultation comments on the disease-specific reference case extension for management of overweight and obesity in adults. We have responded to stakeholders in a hybrid manner, with thematic responses for some comments that share common topics and individual responses (above) for all other comments.

Summary of comments received	Our response and changes
1. Number of subgroups	
We have received seven comments on the theme of the number of analyses required by strata and subgroups specified in the RCE: Five from industry, one from consultancy and one from NHS England. Stakeholder feedback highlight concerns that extensive subgrouping and stratification can create biased or underpowered treatment-effect estimates, make indirect comparisons infeasible, and generate an unhelpfully large number of ICERs that obscure economic conclusions. Stakeholders suggested shifting guidance from “required” to “recommended,” reducing the number of subgrouping expectations, and allowing data to be aggregated when samples are sparse and justification is sound. They also proposed focusing subgroups on factors used for randomisation in the main trial, ensuring alignment between NICE and NHS England, and considering subgroup analyses case-by-case based on the supporting evidence and the medicine’s value proposition.	As specified in the statements regarding population strata, evaluations do not need to include every possible subgroup or strata specified in the statements if certain groups are not relevant to the decision problem or fall outside the marketing authorisation. However, it is essential to present key differences in cost-effectiveness between strata with Type 2 diabetes mellitus (T2DM), established atherosclerotic cardiovascular disease (ASCVD), or neither condition. Particularly, presenting outcomes for subgroups with both T2DM and ASCVD can support the prioritisation of treatment based on those with the highest clinical need. Conversely, the benefits to these patients should not inform the cost-effectiveness of a treatment in people who have neither. While it may not be possible to estimate subgroup-specific treatment effects for each relevant subgroup, model developers should clearly state the assumptions applied when subgroup-specific estimates are unavailable. Testing for heterogeneity of effect between strata is suggested. Other parameters, such as baseline risk and health-state costs, should appropriately vary by subgroup. Splitting analyses by obesity subtype is recommended where informative but is not a mandatory requirement.
2. ASCVD as a population stratum	
We have received three comments on the theme of ASCVD as a population stratum: all three comments were from industry.	As specified in the statements regarding population strata, evaluations do not need to include every possible subgroup specified in the statements if certain groups are not relevant to the decision problem or fall outside the marketing authorisation.

Stakeholders considered that stratifying analyses by ASCVD status is neither feasible nor valid, and that ASCVD should be recommended rather than required, or removed altogether from the framework. They considered that ASCVD is not an established treatment-effect modifier for weight-loss outcomes and is primarily relevant only to cardiovascular endpoints. Post-hoc subgrouping by ASCVD status would lead to insufficient sample sizes, loss of randomisation, and lack of statistical power, and that there is a scarcity of robust data in secondary prevention settings. ASCVD is already subject to standalone HTA evaluation.	There is demonstratable heterogeneity in ASCVD and non-ASCVD population groups, especially in regard to risk of further ASCVD events, life expectancy, which have a subsequent impact on costs and quality of life. As such, interventions would be expected to have different cost effectiveness across these groups. Where data is not available for treatment effects in a ASCVD population, it is not appropriate to use data from non-ASCVD groups, and it is not appropriate to estimate ICERs and make guidance for treatments in a ASCVD group using evidence from non-ASCVD groups. Conversely and more importantly, the benefits to people without ASCVD are likely to be less than those with ASCVD, so those benefits should not be attributed to the wider population. We now recommend using direct evidence where available to model the risk of events (including recurrent events), rather than via changes in surrogate marker outcomes and risk equations, as we acknowledge that the mechanism of action of some interventions means that there is a treatment effect beyond the indirect impact of reducing BMI. ASCVD is subject to a separate standalone HTA assessment; however, it is within the scope of this statement as this document is applicable to treatments for obesity including whether managing obesity is the primary indication or for risk prevention in an obesity population. We maintain that it is required to model this stratum separately to non-CVD populations and no changes have been made to statements about population strata.
Summary of comments received	**Our response and changes**
3. Evidence hierarchy	
We have received four comments on the theme of evidence hierarchy. Two from industry and two from EAGs. Stakeholders noted that the draft reference case extension (RCE) appeared to prioritise modelling treatment effects using surrogate outcomes and risk prediction tools, with directly observed outcomes used mainly for validation/calibration. They considered this to reverse the evidence hierarchy	We agree that high-quality, directly measured health outcomes should be prioritised where available, in line with evidence-based medicine principles. The intention of the original wording was to support long-term extrapolation in situations where direct evidence is limited; however, we recognise that it could be interpreted as giving greater weight to risk-factor-based modelling than to directly observed outcomes. In response, we revised RCE statement to explicitly state the hierarchy of evidence, prioritising directly measured outcomes where available for all relevant comparators. We also revised RCE statement to clarify that risk-factor-based modelling is used only where

expected under evidence-based medicine, where directly observed clinical outcomes should be prioritised when available.	directly measured outcomes are unavailable or cannot be applied consistently across comparators, and is not intended to replace directly observed evidence. Together, these revisions re-establish a clear evidentiary hierarchy while retaining the ability to predict outcomes where necessary.
4. The use of surrogate outcomes	
We have received five comments on the theme of surrogate outcomes, including the definition and its use. Two from industry and three from EAGs. Stakeholders noted that the use of the term "surrogate outcomes" was ambiguous and could be interpreted as referring to validated causal surrogate endpoints or risk-factor inputs to risk equations. This created uncertainty about the level of surrogacy assumed in the RCE and the role of these variables in the model.	We agree that the term "surrogate outcomes" was ambiguous and could be misinterpreted, particularly given its established meaning within evidence-based medicine, which distinguishes between two levels: level one referring to validated causal surrogate endpoints, and level two referring to a consistent association between a surrogate and the final outcome. In the context of obesity modelling, where direct evidence is often limited, modelling commonly relies on associative relationships between risk factors and downstream outcomes, rather than on fully validated surrogate endpoints. In this RCE, we encourage the use of risk factors (such as body weight, HbA1c, blood pressure, and lipid levels) as inputs to risk prediction tools when directly observed outcomes are unavailable. We have now revised RCE statement to clarify that these variables are treated as risk-factor inputs to validated risk prediction tools or risk equations. This revision clarifies the level of surrogacy assumed in the RCE and avoids implying causal surrogacy where this is not supported by the evidence. The listed risk factors are "recommended" rather than "required" and not exhaustive. These should be consistent with the inputs required by the chosen risk prediction tool or risk equation. We have also clarified that for each outcome to be included in models, there needs to be either evidence of an association between weight loss and improved outcome independent of other factors or else direct evidence from randomised trials.
5. Risk Equations	
We have received 11 comments on the theme of risk equations, including the selection of risk prediction tools and the role of validation and calibration when using risk equations. Nine from industry, one from individual and one from EAGs.	We acknowledge that robust, stratum-specific validation evidence for risk prediction tools is often unavailable, and that providing prescriptive statements on specific risk equations would require further systematic research. As such, the guidance does not recommend specific risk prediction tools. Instead, it emphasises that the use of validated risk equations should be clearly justified, with preference given to tools applicable to the English NHS context, for example QRisk3. The identification and assessment of preferred risk prediction tools have been noted as an area for future research.

Stakeholders noted that the draft RCE required the use of validated risk prediction tools but provided limited clarity on how such tools should be selected or how to proceed when validation in specific population strata is unavailable. They expressed concern that this could lead to inconsistent choices across submissions and increased uncertainty. They requested clearer guidance on how to select risk prediction tools and how validation or calibration should be undertaken when stratum-specific evidence is lacking.	We revised the RCE to clarify that risk-factor-based modelling is used where appropriate, and that the choice of risk factors is driven by the selected risk prediction tool, rather than requiring a fixed or minimum set of inputs. We also revised RCE statement to clarify the role of validation and calibration as a corrective step to be informed by observational data.
6. Applicability & Terminology (Population, Subgroups, Strata)	
We have received six comments regarding the confusion of the stratum and unclear terminology. Three from consultancy, one from EAG, one from industry and one from an individual. Stakeholders raised concerns about the introduction and use of the term "population stratum", noting that it was unclear how this differed from the decision population or clinically defined subgroups, and that it could be interpreted as requiring stratum-specific evidence that is often unavailable. They also highlighted ambiguity in the use of the term "English NHS population" and requested clearer, consistent wording.	We have defined stratum in the glossary, as being groups that cannot be pulled together in an economic evaluation. We have specified 8 strata at the beginning of the reference case. Whenever, we talk about strata or stratification it is these 8 strata that we are referring to. For any other groups we refer to them as subgroups not strata. We have clarified that specific relative treatment effects for each stratum might not be necessary. But there needs to be testing for heterogeneity of effect between strata. Separate baseline risks should be sought for each stratum, as there is expected to be heterogeneity.
7. Mortality	
We have received three comments on mortality, two from industry and one from an individual. Stakeholders asked NICE to give more detailed guidance on the mortality modelling approach, such as data source, mortality multipliers and competing mortality risks. One stakeholder was concerned that mortality effects might be under-estimated.	We have noted that mortality rates should ideally be from a single source and should be by weight or weight category AND presence of or history of a relevant health event. Ideally, they should also account for age-sex too. If so, the mortality multipliers can be derived and applied to individual patients not just sub-populations. We have added this to Table 3 with suggested real-world data sets. To mitigate potential under- or over-estimating of mortality effects, we have added a statement that trial data on all-cause mortality should be used to validate and if necessary to calibrate the aggregate mortality predicted by the model.