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

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Overview

This disease-specific reference case extension outlines standardised modelling approaches to inform health economic evaluations of interventions for managing overweight and obesity and reducing associated comorbidities in adults. It applies to all cost-utility analyses developed to inform NICE guidelines, technology appraisal guidance, and HealthTech evaluations. Where relevant, elements of this disease-specific reference case extension can also apply to other types of economic evaluations such as cost-comparison analyses. Adherence to this disease-specific reference case extension should be attempted where possible while taking into account the specific decision problem under evaluation. It should be read alongside the following NICE manuals (including the reference case) for:

- guidelines – including section 7.4
- health technology evaluations (which covers technology appraisals) – including section 4.2
- HealthTech programme – including section 2.1.19

For further details on developing and implementing disease-specific reference case extensions, including the basis for 'required' and 'recommended' statements and how the disease-specific reference case extension should be used, please refer to NICE's position statement on use of disease-specific reference models in economic evaluations.

Reference case extension

1.1 Population

1.1.1 Results should be stratified (that is, reported separately and not combined) by baseline presence or absence of type 2 diabetes mellitus (T2DM), baseline presence or absence of atherosclerotic cardiovascular disease (ASCVD) and whether the population is living with overweight or obesity at baseline (required):

- overweight, no T2DM and no ASCVD
- overweight, ASCVD and no T2DM
- overweight, T2DM and no ASCVD
- overweight, T2DM and ASCVD
- obesity, no T2DM and no ASCVD
- obesity, ASCVD and no T2DM
- obesity, T2DM and no ASCVD
- obesity, T2DM and ASCVD.

Only the stratum or strata relevant to the intervention's target population need be modelled. Where the target population is more specific than a single stratum, only that specific population should be modelled.

1.1.2 Further subgrouping should be undertaken to reflect differences in baseline risk of events and to capture existing thresholds for surgical interventions and medications – see paragraphs 1.1.4 to 1.1.6. (recommended)

1.1.3 The population in the model should be subgrouped by body mass index (BMI) category, at least in a sensitivity analysis. The

categorisation should be done by ethnicity when individual patient data is available as per table 1. (recommended)

Table 1: BMI categories by ethnic group

Category	BMI range: white (kg/m^2)	BMI range: South Asian, Chinese, Middle Eastern, Black African, and African-Caribbean (kg/m^2)
Healthy weight	18.5 to 24.9	18.5 to 22.9
Overweight	25 to 29.9	23 to 27.4
Obesity class 1	30 to 34.9	27.5 to 32.4
Obesity class 2	35 to 39.9	32.5 to 37.4
Obesity class 3	40 or more	37.5 or more

Source: NICE CKS: Obesity diagnosis, identification and classification

The healthy weight category would not be included as a baseline weight category, but it is relevant for later modelling.

1.1.4 For strata containing people without either T2DM or ASCVD, subgrouping by type or number of comorbidities (such as dyslipidaemia, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnoea or prediabetes) should be undertaken as part of the sensitivity analyses. (recommended)

1.1.5 For strata containing people with T2DM or ASCVD or T2DM and ASCVD, subgrouping by presence or absence of chronic kidney

disease (CKD) or chronic heart failure (CHF) should be undertaken as part of the sensitivity analyses. (recommended)

1.1.6 Regression analysis by BMI or BMI category and type or number of comorbidities should be undertaken where possible. (recommended)

For the rationale for these paragraphs see the **section on population**Population.

1.2 Intervention and comparators

1.2.1 The model should include all potentially relevant comparators that are established practice in the NHS for managing weight and reducing weight-related comorbidities, including those already recommended by NICE for obesity and overweight management. (required)

1.2.2 Behavioural interventions alone, that is, a reduced-calorie diet and increased physical activity, are a relevant comparator and should be included in the model. (required)

1.2.3 As a minimum, new medicines should also be compared with (required):

- medicine(s) established in NHS clinical practice (except where contraindicated)

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)

1.2.5 As a minimum, new digital technologies should also be compared with (required):

- existing digital technologies established in NHS

1.2.6 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/m^2 and 39.9 kg/m^2 with a significant health condition that could be improved if they lost weight, or
- adults with a BMI of 40 kg/m² or more.

1.2.7 If an intervention or comparator is indicated alongside a behavioural intervention such as 'a reduced-calorie diet and increased physical activity' then this should be captured in the model for the duration of the treatment. (required)

1.2.8 When comparing an intervention to behavioural interventions alone, different intensities of behavioural interventions should be considered in sensitivity analyses. (recommended)

1.2.9 When comparing an intervention to behavioural interventions alone, a sensitivity analysis should be conducted with the behavioural intervention defined as a minimal intervention of GP advice once a year about diet and exercise. This reflects the limited availability of services specifically for overweight and obesity. (required)

1.2.10 For the base case analysis, background treatments should reflect established NHS practice relevant to the stratum, for example, as detailed in the following NICE guidelines (required):

- obesity and overweight management
- type 2 diabetes mellitus in adults
- cardiovascular disease: risk assessment and reduction, including lipid modification.

In a sensitivity analysis, they should reflect those used in the corresponding trial data. (required)

For the rationale for these paragraphs see the **section on intervention and comparators**.

1.3 Model structure and health states

1.3.1 A state transition modelling approach, either as a cohort or individual patient-level simulation (IPS), would be suitable. However, when justified, alternative modelling approaches can be used if they can be easily interrogated and validated and capture all important differences in costs or outcomes between the intervention and comparator. (required)

1.3.2 Where a cohort model is used, tunnel states should be included to capture dependencies between events. (recommended)

1.3.3 A lifetime horizon should be used where an intervention is expected to have an effect on costs and outcomes over the person's lifetime. (required)

1.3.4 Cycle length should not exceed 1 year. Transformations and costs and utilities should generally be half-cycle corrected. However, front-loading of some high-cost items such as admissions or surgical procedures might be needed to ensure that the opportunity cost is captured. (required)

1.3.5 If a cohort approach is taken, then subgrouping by age and sex as well as body mass index (BMI) category and comorbidity is advised (unless there is evidence of linearity of effects) with weighted-

average costs and quality-adjusted life years (QALYs) calculated. (recommended)

1.3.6 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'
- 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: 'healthy weight' or 'overweight' or 'obesity'
- line of treatment (if applicable)
- 'alive' or 'dead'.

1.3.7 For strata containing people with T2DM or ASCVD or T2DM and ASCVD, the health states should also capture the following: (recommended)

- chronic kidney disease (CKD) status: no CKD or stage 1 to 4 CKD or stage 5 CKD
- presence or absence of chronic heart failure.

1.3.8 The following movements between health states should be included: (recommended)

- remission and recurrence of prediabetes
- progression of T2DM status
- progression of ASCVD status
- change in weight category

- all live states to dead (by definition).

1.3.9 The following movements between health states should not be included: (required)

- remission of T2DM (unless there is direct evidence for the intervention)
- remission of ASCVD status.

1.3.10 The costs and QALY losses of the following health events should be included in the model, but they do not necessarily need to be health states: (recommended)

- obstructive sleep apnoea
- knee replacement
- bariatric procedure (unless an intervention or comparator in the model), with procedure type clearly defined and justified
- treatment-related adverse effects (non-serious adverse effects with an incidence of more than 5% for each intervention and any serious adverse effects) (required)
- discontinuation.

1.3.11 The following health events should be considered for inclusion in a sensitivity analysis if there is direct evidence of a treatment effect: (recommended)

- metabolic dysfunction-associated steatotic liver disease (MASLD)
- cancer (breast, colorectal, kidney, liver and womb*)*
- CKD.

For the rationale for these paragraphs see the **section on model structure and health states**.

1.4 Clinical parameters and variables (treatment effects and risk prediction)

1.4.1 The effectiveness of interventions should be modelled in terms of weight changes and changes to surrogate outcomes linked to the health outcomes and health events included in the model structure. (required)

1.4.2 The weight changes and other surrogate outcomes should be specific to the population stratum as well as the treatment and relevant to an English NHS population. (recommended)

1.4.3 The following surrogate outcomes should be included as a minimum for predicting change in the incidence of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM): (recommended)

- weight and body mass index (BMI)
- systolic blood pressure
- HbA1c
- cholesterol (high-density lipoprotein and low-density lipoprotein)
- estimated glomerular filtration rate (eGFR).

1.4.4 The selection of validated risk prediction tools or risk equations to estimate modelled outcomes and events should be justified. (required)

1.4.5 Risk prediction tools should be validated in the population specific to the stratum and relevant to an English NHS population. (recommended)

1.4.6 Annualise risks to ensure they do not overestimate outcomes and events. (required)

1.4.7 Where available, high-quality directly measured health outcomes (either from trial data or real-world evidence) should be used to validate and, if necessary, calibrate predicted outcomes from risk equations or risk prediction tools. (required)

1.4.8 For treatment-related adverse effects that are otherwise rare, the absolute rates should be taken from trial data or real-world evidence. For more common adverse effects a baseline from real-world evidence should be applied to relative effects from trial data. (recommended)

1.4.9 Use sensitivity analyses to explore the impact of length of time of living with overweight or obesity on future outcomes. (recommended)

For the rationale for these paragraphs see the **section on clinical parameters and variables (treatment effects and risk prediction)**.

1.5 Clinical parameters and variables (effects over time and mortality)

1.5.1 Capture treatment effect over time and reflect uncertainty as follows: (required)

- apply consistent assumptions on weight trajectory across all interventions to avoid bias in the relative treatment effect
- model the rate of weight change over time that is specific to the population stratum and treatment and relevant to an English NHS population.
- incorporate scenario analyses that explore uncertainty in long-term treatment effects after the trial observation period, including:
    - applying the same natural history weight gain to both interventions and comparators
    - assuming no natural history weight gain in interventions and comparators
    - exploring partial waning of treatment effect on weight loss over time.

1.5.2 Treatment duration or discontinuation should be included in the model for interventions and comparators including behavioural intervention only comparators. This should include discontinuation or stopping of treatment because of adverse effects, treatment inefficacy or remission. (required)

1.5.3 Discontinuation should affect intervention resource use. Also, beyond trial follow-up, relative treatment effect should be reduced

to reflect discontinuation or treatment effects should apply only to people continuing with the treatment. (required)

1.5.4 When medicines have been discontinued, NHS resource use associated with concomitant behavioural interventions should stop unless there is evidence that behavioural interventions without medicine have continued in clinical practice in England. (required)

1.5.5 Consider modelling treatment discontinuation over time as follows: (recommended)

- rate of discontinuation over time should be specific to the population stratum and treatment and relevant to an English NHS population.
- baseline discontinuation rates should be sourced from real-world evidence and relative differences between interventions from trial data.

1.5.6 Include threshold analyses to identify optimal treatment durations. (recommended)

1.5.7 Account for weight regain after treatment discontinuation, using evidence from long-term studies where available: (required)

- where long-term studies for the intervention are not available, use evidence for other treatments with a similar mode of action or clinical expert opinion
- rate of weight gain over time should be specific to the population stratum and treatment and relevant to an English NHS population
- include scenario analyses informed by clinical opinion to test the impact of different regain rates or durations, for example, return to initial baseline weight after a specific number of years of discontinuation.

1.5.8 Use a consistent mortality modelling approach: 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)

- Where possible, mortality rates (cardiovascular mortality and non-cardiovascular mortality) should be specific to the population stratum and health state and relevant to an English NHS population

- Do not apply BMI all-cause mortality multipliers to non-cardiovascular mortality and then add cardiovascular mortality on top. This will over-estimate the treatment effect. The BMI multipliers would have to be specific to non-cardiovascular mortality.

- Where BMI-adjusted mortality is used, granularity in BMI categories is preferred: age-specific hazard ratios reflect the non-linear and age-dependent relationship between BMI category and mortality risk. (recommended)

1.5.9 Use sensitivity analyses to explore the impact of length of time of living with overweight or obesity on mortality. (recommended)

For the rationale for these paragraphs see the **section on clinical parameters and variables (effects over time and mortality)**.

1.6 Measuring and valuing health effects

1.6.1 Baseline utility should be measured using EQ-5D based on age, body mass index (BMI) and sex and should change over time with

age and BMI. Utility decrements should then be applied to specific events and comorbidities. (required)

1.6.2 The best source for utilities would be a single dataset that controls for weight, comorbidity and other variables such as age and sex. If that is not available then, to avoid double-counting, ensure that the source for weight controls for comorbidities or the source for comorbidities controls for weight. (required)

1.6.3 Mean EQ-5D scores for each intervention in the clinical trials can be used to calibrate the mean quality-of-life treatment effect in the short-term (at trial follow-up), ensuring not to double count health-related quality of life improvements from the reduced incidence of progression or adverse effects. (recommended)

1.6.4 Utility decrements for treatment-related adverse effects should be captured in the model. For example, include gastrointestinal (GI) adverse effects such as nausea, diarrhoea and constipation for medicines. (required)

For the rationale for these paragraphs see the **section on measuring and valuing health effects**.

1.7 Cost and healthcare resource use identification, measurement and valuation

1.7.1 The cost of medicines should include dispensing, refrigeration, waste disposal and delivery costs, if applicable. (required)

1.7.2 For behavioural interventions, whether as a comparator or used concomitantly with medicines, resource use should reflect current NHS practice in the base case. In a sensitivity analysis, this should be based on resource use associated with the relevant trials. (required)

1.7.3 Health state and event costs, including costs associated with treatment-related adverse effects, should align with clinical practice

and where appropriate be specific to the population stratum and be sourced from the English NHS. (recommended)

1.7.4 Background comorbidity costs and acute event costs can overlap. Adjustments should be made to cost estimates to ensure that the cost of care is not over-estimated. (required)

1.7.5 Resource use for modelled comorbidities should consider duration of comorbidity, with different costs for managing newly diagnosed comorbidities versus those for managing established comorbidities. (recommended)

1.7.6 For type 2 diabetes mellitus (T2DM) costs, cohort studies are recommended. For example, the UK Prospective Diabetes Study (UKPDS), which include the cost of consultations, visits, admissions and procedures associated with diabetes-related complications. (recommended)

For the rationale for these paragraphs see the **section on cost and healthcare resource use identification, measurement and valuation**.

1.8 Equality and other considerations

1.8.1 Living with obesity (unlike living with overweight) has a higher incidence in areas with greater socioeconomic deprivation. Where appropriate, for strata that include people living with obesity, a distributional cost-effectiveness analysis could be undertaken with results presented by deprivation quintile group. (recommended)

1.8.2 The following benefits and risks might be difficult to fully capture quantitatively in the modelling, therefore consider qualitatively the

impact interventions for the management of overweight or obesity, on: (recommended)

- costs and health-related quality of life beyond trial follow-up associated with mental illness, for example, depression and anxiety
- health inequalities related to protected characteristics, for example, ethnicity or disability such as severe mental illness, autism or learning disability, because incidence of obesity is higher in these groups
- access to other treatments, for example, organ transplants
- treatment-related outcomes, for example, fertility
- the health of unborn children.

For the rationale for these paragraphs see the **section on equality and other considerations**.

Rationale and supporting information

Population

Rationale for section **1.1**

Modelling needs to reflect that people with specific comorbidities will have different levels of risk of health events and capacity to benefit from treatments for overweight and obesity and will be on different care pathways.

Type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) were identified as key comorbidities for people living with overweight and obesity. Therefore, it was agreed that results should be stratified according to whether people have these conditions. This also reflects how treatments are recommended in NICE's guideline on type 2 diabetes in adults and NICE's technology appraisal guidance on tirzepatide for treating type 2 diabetes, and in a NICE technology appraisal in progress on semaglutide for

preventing major cardiovascular events in people with cardiovascular disease and overweight or obesity.

Stratification by body mass index (BMI) category was considered appropriate by the clinical experts because:

- the risk of developing comorbidities is linked to BMI category
- it allows for any differences in treatment effect by BMI category to be identified and so
- allows for recommendations to be developed that capture this.

Clinical experts and patient advocates debated using BMI compared to waist circumference for stratifying the population of interest. They highlighted the importance of waist circumference measurement and its use in waist to height ratio calculations, particularly for people with a BMI of less than 35 kg/m^2 as per NICE's guideline on overweight and obesity management, but noted that it is unlikely to be useful for modelling purposes as currently there are no risk equations that use this measure to estimate risk of developing associated comorbidities (see section 1.4).

Stratifying obesity in adults into 3 groups as outlined in the section on classifying obesity in adults in NICE's guideline on overweight and obesity is desirable. However, that would have increased the total number of strata from 8 to 12. To keep it manageable, only stratification between overweight and obese is 'required'. Subgrouping the obesity strata further although desirable, might not be essential for all cost-utility analyses and so this has been rated as 'recommended'.

Ethnicity-specific BMI thresholds were included to reflect evidence reported in NICE's guideline on overweight and obesity management that certain ethnic populations (for example, South Asian, Chinese, Middle Eastern, Black African and African-Caribbean) have a higher cardiometabolic risk at lower BMI levels than white populations. Where individual patient data is available, it

was agreed that subgrouping should be done by ethnicity, taking into account the ethnic-specific BMI thresholds.

Stratification by both BMI category and comorbidity allows the impact of interventions on cardiovascular events and T2DM to be captured.

The number and type of comorbidities in the population are important as they influence baseline risk of morbidity and mortality. Treatment may result in a greater reduction in risk for certain subgroups. Sensitivity analyses that explore the cost-effectiveness of interventions in different population subgroups defined by both type and number of comorbidities will help identify the populations that will gain the greatest benefit. Where possible, health economic modellers are encouraged to undertake regression analyses by BMI category and comorbidity combinations.

It was agreed that populations without T2DM or ASCVD should be grouped using other comorbidities such as dyslipidaemia, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnoea and prediabetes. This is in line with NICE's technology appraisal guidance on semaglutide and tirzepatide for managing overweight and obesity. However, it was considered these might have less power to predict health outcomes within the 6 population strata that have T2DM or ASCVD or T2DM and ASCVD and so subgrouping using these additional comorbidities was not recommended here.

Chronic kidney disease (CKD) and chronic heart failure (CHF) have been included as subgroups for the population strata containing people with T2DM or ASCVD or T2DM and ASCVD. This was to align with modelling undertaken for the medicines update of NICE's guideline on type 2 diabetes in adults and to reflect the increased prevalence of these conditions in these populations (Dawson et al. 2023, Koye et al. 2018, Lee et al. 2024, Panchal et al. 2024).

It is acceptable to only include the strata or stratum that reflect the eligible target population for the intervention of interest. For example, if an intervention was targeting people with a BMI of 40 kg/m^2 or more and ASCVD, then only this stratum could be presented.

Intervention and comparators

Rationale for section **1.2**

To ensure consistency and relevance across cost-utility analyses, all potentially relevant comparators that are established practice in the NHS for managing weight and reducing weight-related comorbidities, including those already recommended by NICE, should be included. These comparators represent the spectrum of treatment intensity and allow for meaningful comparisons of cost-effectiveness.

The inclusion of assessment for bariatric procedures as a comparator reflects NICE's guideline on overweight and obesity and acknowledges the clinical and cost-effectiveness of surgical interventions for individuals with obesity. This has been included as a 'recommended' rather than 'required' statement as the strength of NICE's recommendations on assessment for bariatric procedures vary, depending on population BMI.

It is important to note that not all those assessed for bariatric procedures will receive it and therefore the model should account for this using published data or real-world evidence.

There are several bariatric procedures available in the NHS. These vary in terms of their invasiveness, reversibility, effectiveness, complications and costs. The comparator procedure should be clearly defined in the model to ensure appropriate effectiveness data and costs are applied. Justification for the choice of bariatric procedure should be provided and ideally should reflect established NHS practice. Different surgical procedures may be appropriate for different population strata. Where surgical innovation is involved, factors such as learning curve, organisational impact, incremental innovation and dynamic pricing should be incorporated at least in sensitivity analyses, where possible (Drummond et al. 2009, Drummond et al. 2018). The provision of other interventions while people are waiting to receive bariatric procedures should be considered for inclusion in the model.

In line with clinical practice and NICE guidelines, if an intervention is indicated alongside a behavioural intervention, then this should be captured in the model. However, the intensity and structure of behavioural interventions can vary significantly, making it challenging to achieve consistency between models. To address this, different intensities of behavioural interventions should be explored in sensitivity analyses, with each behavioural intervention clearly described and costed. This should be done separately for the concomitant and standalone behavioural interventions.

When comparing an intervention to behavioural interventions alone, sensitivity analyses should consider a minimal intervention of GP advice once a year to reflect the limited availability of services for overweight and obesity in the NHS.

For strata that include individuals with T2DM or ASCVD, standard background treatment for those conditions should be included and costed, ensuring that models reflect realistic treatment pathways and avoid underestimating costs or overestimating incremental benefits. In the base case these background treatments should reflect those used in the NHS.

At the time of writing, background treatment for T2DM included metformin and an SGLT2 inhibitor, except where contraindicated (see NICE's draft guidance for T2DM). For people with ASCVD, background treatment should include lipid-lowering treatment and other relevant treatments. However, background treatment in trials may not reflect established clinical practice in the NHS, and so a sensitivity analysis should reflect background treatments used in the corresponding trial evidence to ensure they are aligned with the effectiveness data.

Model structure and health states

Rationale for section **1.3**

A state transition modelling approach, either cohort-based or individual patient-level simulation (IPS), was considered suitable by health economic modellers.

State transition models are well-suited to chronic disease modelling and have been widely used in obesity and related comorbidities (see appendix B). They offer relative transparency to more complex modelling approaches such as discrete event simulations, ease of use and are able to capture disease progression over time.

State transition models can be used for a wide range of intervention types for managing obesity, such as medicines, surgery and behavioural interventions, and allow for isolation of specific benefits where needed to support transparent decision-making.

Cohort models are simpler than IPS models but may require subgrouping by age and sex, as well as BMI category and comorbidity to reflect population heterogeneity. IPS models allow for tracking of individual patient histories, which is particularly important in obesity where events such as treatment discontinuation, bariatric procedures or cardiovascular events can occur at varying times and influence future risks. IPS models can better capture dependencies between events, which are difficult to represent in memoryless cohort models. If a cohort model is used, tunnel states should be considered to address these limitations.

A lifetime time horizon is appropriate to capture the full impact of obesity interventions on health outcomes and costs. This is because many obesity interventions, whether medicines, surgery or behavioural interventions, have long-term impacts on health outcomes, costs and survival. Obesity is associated with chronic conditions such as type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD), which develop over time and can persist throughout a person's life. Therefore, a sufficiently long-time horizon is needed to capture all meaningful differences in costs and outcomes between treatment options.

Obesity is associated with a wide range of health conditions, some causally linked and some potentially contributing to obesity itself, such as polycystic ovary syndrome. Certain comorbidities, such as T2DM and ASCVD, can significantly alter treatment pathways and long-term outcomes. Therefore,

economic models should include a carefully selected set of comorbidities and health events that reflect the burden of obesity. The inclusion of these should be guided by the following criteria:

- strong evidence of an association with obesity
- clinical plausibility that the intervention affects the risk of developing the comorbidity or health event happening
- availability of sufficient data to support inclusion without relying on speculative assumptions
- evidence of it having a meaningful impact on costs, quality of life or risk of other outcomes (for example, mortality)
- their relevant to high-quality core outcome sets to ensure consistency and alignment with broader clinical and research standards (for example, International Consortium for Health Outcome Measure's patient-centred outcome measures for adults living with obesity).

A minimum set of health states to be included in economic model have been provided. Only events or outcomes that have been directly measured or where there are validated risk equations (see paragraph 1.4.4 for details on the use of validated risk equations) should be included. These should reflect the most common and impactful obesity-related comorbidities.

Transitions in the model should reflect realistic disease trajectories to ensure clinical credibility and avoid overestimating intervention benefits. They are essential because they reflect the natural history of obesity and its complications. The included transitions are supported by robust evidence and are key drivers of long-term costs and health outcomes.

While remission of T2DM may occur in specific contexts, assuming reversal without evidence risks inflating QALY gains and underestimating costs, leading to biased cost-effectiveness estimates. Therefore, remission of T2DM should not be modelled unless there is direct evidence from the intervention under evaluation.

Reversal of ASCVD status should not be modelled as it is largely irreversible in clinical terms. This approach maintains clinical plausibility and protects against over-optimistic projections.

Other events, while not needing to be captured as health states in the economic model, have significant cost and utility implications and so should be included as health events in the model. These were identified by reviewing previous obesity health economic models (as outlined in appendix B) and after discussions with clinical experts and patient advocates. The following health events should be included for the reasons given:

- obstructive sleep apnoea – because it is prevalent in people with obesity and contributes to reduced quality of life and increased healthcare utilisation
- knee replacement – because it is a costly treatment for osteoarthritis, a common weight-related condition
- bariatric procedures – because of its substantial impact on weight, comorbidities and long-term costs.
- all serious adverse effects and non-serious adverse effects that occur in more than 5% in each intervention – based on clinical trial reporting standards and partly reflecting the inclusion criteria in NICE's technology appraisal guidance on tirzepatide for managing overweight and obesity.

The inclusion of these events, as well as discontinuation of medication, should help ensure that models capture the full burden of obesity and the real-world consequences of treatment. They are all 'recommended' for inclusion, with the exception of treatment-related adverse effects, which is 'required' because, unlike the other events, it is relevant for all assessments.

Some health events are recommended for inclusion in sensitivity analyses if there is emerging or partial evidence of a treatment effect. These include:

- Metabolic dysfunction-associated steatotic liver disease (MASLD): Included in the model for NICE's technology appraisal guidance on tirzepatide for managing overweight and obesity due to trial data but not included in NICE's technology appraisal guidance on liraglutide or semaglutide for managing overweight and obesity due to lack of demonstrated impact. Inclusion should be evidence-driven to avoid speculative modelling.

- Cancer: While obesity is a known risk factor for several cancers, there is limited evidence demonstrating a reduced risk of cancer following weight loss. In NICE's technology appraisal guidance on liraglutide for managing overweight and obesity, when cancer was included in the economic model, the incremental cost effectiveness ratio (ICER) increased slightly, since the cost of cancer treatment in the extra months of life was greater than the benefits of a modest reduction in the incidence of cancer. The reverse was true for a scenario with a subgroup with a high risk of cancer at baseline. Either way, the inclusion of cancer is not recommended unless there is evidence of a reduction in the incidence of cancer with weight loss.

- Chronic kidney disease (CKD): The link between obesity and CKD is well established, and there is some evidence that incretin agonists may improve renal outcomes via both direct effects (including glucose lowering in those with diabetes and other tissue effects) and indirect effects (via weight loss). However, the magnitude and mechanism of effect remain uncertain, and ongoing trials such as REMODEL (Cherney et al. 2025) or SURMOUNT-MMO (Lam et al. 2025) may clarify this. Until then, CKD should be included cautiously especially in population strata that have neither T2DM nor ASCVD at baseline but can be tested in sensitivity analyses. The reason for the inclusion of CKD for population strata with T2DM or ASCVD or T2DM and ASCVD was due to the increased risk of CKD in these subpopulations. In addition, CKD

was included to ensure consistency with the modelling undertaken in the medicines update of NICE's guideline on type 2 diabetes in adults.

These events were not included in the minimum health state set because of insufficient direct evidence of treatment effect, uncertainty in causal pathways and potential for modelling complexity or bias. This flexible approach ensures that models remain evidence-based, while allowing opportunity to incorporate new data as it becomes available.

Several additional obesity-related health outcomes such as reproductive health, mental health, chronic lower back pain and inflammatory conditions including arthritis were discussed at workshops involving clinical experts, patient advocates, health economic modellers, industry stakeholders and commissioners. They were not included in the minimum health states or events because there was insufficient direct evidence of treatment effect and concerns with the potential for modelling complexity and double counting of impact on quality of life. It was agreed that these additional health outcomes could be captured qualitatively. 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.

It was noted that for populations with metabolic dysfunction-associated steatotic liver disease (MASLD) at baseline, consideration of additional health states may be necessary. Some guidance is available specifically for metabolic dysfunction-associated steatohepatitis (MASH) – see NICE's health technology assessment innovation laboratory report on evaluating MASH treatments.

Clinical parameters and variables (treatment effects and risk prediction)

Rationale for section 1.4

Trials may only report limited surrogate outcomes and lack long-term data, which is often the case for behavioural and digital interventions, it is

necessary and appropriate to estimate treatment effects using validated risk equations or prediction tools. A summary of risk equations and risk prediction tools used in previous obesity models is reported in appendix B.

In such cases, the effectiveness of interventions should be modelled in terms of changes in weight and other surrogate outcomes (for example, blood pressure, HbA1c levels and cholesterol levels) that are linked to the outcomes and events included in the model structure. These surrogate outcomes are aligned with the cardiometabolic risk outcomes highlighted in the International Consortium of Health Outcome Measures' patient-centred outcome measures for adults living with obesity. This approach is pragmatic, widely used in health economic modelling, and allows for the estimation of long-term health and cost outcomes based on short-term or intermediate-term clinical data.

Where available, directly measured clinical outcomes should be used in sensitivity analyses to validate and, if necessary, calibrate predicted outcomes from risk equations. Direct evidence of intervention effect on comorbidity progression (such as atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM)) or health events is particularly important for interventions that may have effects beyond weight loss, such as medicines that influence metabolic or cardiovascular outcomes through additional mechanisms (Sattar et al, 2025).

Active registries, for example the National Bariatric Surgery Registry and National Obesity Audit, or NHS data accessed via secure data environments may be appropriate sources of real-world evidence depending on the specific data needs.

Emerging evidence suggests that the length of time living with overweight and obesity, has a significant impact on future health outcomes, particularly for conditions such as ASCVD, T2DM, and osteoarthritis (Krüger et al. 2025, Zeng et al. 2023). People with these conditions may carry a residual risk from having them even after substantial weight loss, due to irreversible physiological damage accumulated over time. For example, long-term obesity can accelerate atherosclerosis and joint degeneration, which are not fully

reversed by subsequent weight reduction. This is especially relevant for mechanical outcomes like osteoarthritis, where cumulative joint stress from prolonged high BMI may lead to persistent damage. Therefore, ideally risk prediction tools should be based on changes in risk factor over time rather than cross sectional. Current risk prediction tools often rely on cross-sectional BMI measurements and may not adequately capture the long-term impact of living with overweight and obesity.

Where data is available, the impact of length of time living with overweight and obesity on future outcomes should be explored in sensitivity analyses, for example by stratifying between people who have only recently started living with obesity and those that have lived with obesity for much longer.

Clinical parameters and variables (effects over time and mortality)

Rationale for section **1.5**

Risk equations are a pragmatic and widely used approach in obesity modelling. However, they are not designed for causal inference and often do not capture the dynamic nature of treatment effects, such as initial weight loss followed by weight regain. They may also underestimate clinical benefits, particularly for interventions with indirect or multi-system effects (for example, cardiovascular or metabolic improvements independent of weight loss).

Many interventions show an initial weight reduction followed by partial weight regain (Ahmed 2024, Wu et al 2025). Ignoring this trajectory can misrepresent long-term effectiveness. Models should capture treatment effects over time and weight regain patterns, to better reflect the fact that weight loss is rarely sustained at the same level.

Models should incorporate treatment duration or discontinuation for all treatment comparators, including behavioural intervention only comparators. The baseline rates should be taken from real-world evidence and relative differences between interventions from trial data, where available, and reflect their impact on weight and future outcomes. Adverse effect-related discontinuation is common in medicines for weight management.

Discontinuation affects both the duration of treatment benefit, and the likelihood of weight regain.

Many interventions show an initial weight reduction followed by partial weight regain (Ahmed 2024, Wu et al 2025). Ignoring this trajectory can misrepresent long-term effectiveness.

Commissioners highlighted that when medicines were discontinued, the provision of concomitant behavioural interventions also stopped. The costs in the model should reflect this unless evidence of these behavioural interventions continuing without medicine is available.

There was a strong emphasis from clinical experts and commissioners on the value of real-world evidence to validate assumptions about treatment duration, discontinuation and long-term effectiveness. This is because clinical trials often differ from routine practice in terms of population characteristics, adherence and duration of treatment.

Multiple scenarios and sensitivity analyses should be conducted to explore the impact of different assumptions on model outcomes, as there is considerable uncertainty around long-term weight trajectories, especially beyond trial follow-up periods. These should explore both conservative and optimistic assumptions to give an indication of a range of cost-effective estimates.

NICE's technology appraisal guidance on semaglutide for managing overweight and obesity found the medicine to be less cost-effective after 2 years because of its waning effect on weight. Given this, threshold analyses are recommended to find the point at which treatment is no longer cost-effective.

The purpose of capturing discontinuation rates in the model is in part to capture resource usage. However, beyond the trial follow-up it should also be used to modify the treatment effect. If the majority of people have stopped using the medicine (unless this is due to remission) then the treatment effects are not expected to continue beyond the duration of the trial follow-up. The impact of treatment discontinuation on changes to clinical outcomes such as

glycaemic control should therefore be accounted for following treatment discontinuation.

Mortality should be modelled in a way that is methodologically robust and reflective of the underlying epidemiological evidence. A consistent approach should be adopted, whereby models either apply body mass index-adjusted (BMI-adjusted) all-cause mortality ratios or condition-specific mortality ratios. Combining both risk ratios may lead to double-counting and should be avoided unless clearly justified.

Models should recognise that the length of time people have lived with overweight or obesity may increase the risk of mortality even after weight reduction. Assuming full reversal of BMI-related mortality risk may overestimate treatment benefits.

Measuring and valuing health effects

Rationale for section **1.6**

Models submitted in NICE's technology appraisal guidance on liraglutide, semaglutide and tirzepatide for managing overweight and obesity used baseline utility based on age, body mass index (BMI) and sex, with utility decrements applied to specific events.

A study by Luah et al. in 2024 estimated the association between BMI and EQ-5D-5L among the general population in England using data from 2017 and 2018 health surveys. It distinguished utility values by sex and BMI level. It also derived the coefficients for comorbidities such as diabetes, heart and circulatory disease, respiratory disease, musculoskeletal disease, cancer and mental health disorders. This may be a suitable study to inform the baseline utility and capture utility decrements associated with comorbidities in a consistent manner.

EQ-5D data from patients in relevant clinical trials should be used to calibrate the quality-of-life treatment effect in the short-term (at trial follow-up), as direct evidence of quality-of-life improvement is best when it is precise and of high quality.

The most common treatment-related adverse effects reported for incretin agonists were gastrointestinal (GI) events. Clinical experts at the workshop noted that GI events were a key reason for dose titration. Disutilities for treatment-related adverse effects were applied additively in base cases and a multiplicative approach was explored in scenario analyses in previously published technology appraisal guidance. Health economic modellers noted that the choice of approach depends on whether the effects are independent. If disutilities associated with type 2 diabetes mellitus (T2DM), obesity and any other comorbidities show no significant interactions, then an additive approach seems reasonable.

Cost and healthcare resource use identification, measurement and valuation

Rationale for section **1.7**

As noted by the committee for NICE's technology appraisal guidance on tirzepatide for managing overweight and obesity, there is currently uncertainty about the resource use needed for behavioural interventions (reduced-calorie diet and physical activity) both as comparators and concomitant treatments with medication. The importance of exploring the resource use for these interventions in sensitivity analyses was highlighted during the workshops. If real-world evidence is available from implementing tirzepatide (for example, data collected as part of NHS England's interim commissioning guidance on implementation of NICE's technology appraisal guidance on tirzepatide) on the resource use required for concomitant behavioural interventions, then this should be used.

For the cost of comorbidities and acute events, adjustments should be made to ensure that background costs are not double counted. For example, the cost of treating obesity should be subtracted from the cost of treating type 2 diabetes mellitus (T2DM) or atherosclerotic cardiovascular disease (ASCVD) where relevant.

The cost of treating comorbidities often increases over time as more additional comorbidities develop. With T2DM for example, average resource use is likely

to under-estimate costs for advanced disease and over-estimate costs for incident cases. Workshop experts and the committee for NICE's technology appraisal guidance on tirzepatide for managing overweight and obesity advise that attempts should be made to distinguish the costs of early and later disease.

For T2DM costs, the use of cohort studies is recommended. For example, the committee for NICE's technology appraisal guidance on tirzepatide for managing overweight and obesity preferred using UK Prospective Diabetes Study (UKDS) costs, which include the cost of consultations, visits, admissions and procedures associated with diabetes-related complications rather than the company's initial approach of using diabetes-related NHS reference costs and assuming 1 hospital attendance or stay per patient per year.

Equality and other considerations

Rationale for section **1.8**

Obesity is more prevalent in the most socioeconomically deprived quintiles of the population (see NICE's health inequalities briefing report for its guideline on overweight and obesity management and its health inequalities report for its medicines update of its guideline on type 2 diabetes in adults).

Recommending treatments for obesity can potentially help narrow the gap in health outcomes between socio-economic groups. Distributional cost-effectiveness analysis, if applicable, can show the potential impact of an intervention on health inequalities and specifically the health inequality gap in the general population (see the section on distributional cost-effectiveness analysis methods in NICE's health technology evaluations manual). However, the number of adults with obesity in England is very large and so committees should be aware that the opportunity cost associated with accepting a slightly higher ICER could be substantial.

For pragmatic reasons, models inevitably do not cover every effect. A few elements that are unlikely to be captured in economic models were identified

as important by clinical experts, patient advocates, health economic modellers, industry stakeholders and commissioners. These have been highlighted for qualitative consideration outside of the model.

Obesity is associated with mental illness, which can worsen when lost weight is regained (Theodoulou et al. 2023). This was an important outcome highlighted by clinical experts and patient advocates. However, incorporating specific health states around mental illness would be complicated and existing models do not include them. Furthermore, it might be hard to distinguish resource use for mental illness from other background costs. Therefore, this might be considered qualitatively in addition to the model results.

Impact on mental health should be captured by the EQ-5D if measured during trials and used to calibrate model results. Strategies that produce weight loss that is sustained will be the most effective at improving mental health.

Weight management is a key consideration in access to other treatments. Two were identified in the expert workshops: fertility treatment (Boddeti et al 2025, Pandey 2010) and transplant surgery (Ghanem et al 2024).

The methods for distributional cost-effectiveness analysis are not as well developed for other aspects of health inequality, as they are for socioeconomic deprivation. Therefore, these should be considered outside of the model. Health inequalities for people living with disability and for specific ethnic groups have been highlighted based on the NICE's health inequalities briefing report for its guideline on overweight and obesity management and the advice of workshop experts.

Methodology

To inform the development of this disease-specific reference case extension for obesity, the following activities were conducted:

- A pragmatic review of recent health economic modelling approaches used in the evaluation of obesity interventions, drawing on

NICE guidance, publications from other health technology assessment agencies and academic literature. (see appendix B).

- Consideration of epidemiological data on the prevalence of obesity-related comorbidities to support decisions on which conditions should be included in economic models and how they should be represented.

In addition, NICE convened a series of virtual engagement workshops to explore key methodological issues and preferred modelling approaches. Each workshop targeted a specific stakeholder group to ensure a broad range of perspectives:

- first workshop engaged clinical experts and patient organisations to understand clinical pathways and patient priorities
- second workshop focused on health economic modellers, discussing technical modelling challenges and potential solutions
- third workshop brought together industry stakeholders to explore the implications of modelling choices on innovation and market access
- fourth workshop was held with commissioners to gain their perspective on the reference case extension.

Insights from these workshops, along with feedback from a wider stakeholder consultation, informed the recommendations presented in this report. A detailed overview of the workshops is provided in appendix A.

Glossary

Terms used in this document are defined in the NICE glossary and the table below.

Term	Definition
Cohort model	A type of health economic model that follows a group of individuals with shared characteristics through defined health states over time, using average transition probabilities to estimate cost effectiveness of interventions.

Individual patient-level simulation	A modelling approach that simulates outcomes for individual patients rather than a whole cohort. Each simulated patient has unique characteristics and pathways through health states, allowing variability in risks, events, and treatment effects to be captured.
Risk equations	Risk equations are mathematical formulas used to estimate the probability of a health event based on patient characteristics. These equations are often derived from regression models using clinical trial or cohort data and are commonly used in economic models to simulate disease progression or treatment impact.
Risk prediction tool	It uses one or more risk equations and other types of analysis approaches such as algorithms and scores to provide an estimate of a person's risk of a health event.
State transition model	A modelling approach in which a population or individuals move between defined health states over certain time periods. State transition models can be implemented as cohort models or individual-level models.
Stratum	A stratum is a group of population units that are pre-defined based on specific characteristics. Stratification is used to ensure that each group is adequately represented, and each stratum is mutually exclusive.
Subgroup	A subgroup is a set of participants, used to explore differences in outcomes or effects across specific characteristics (e.g. gender, comorbidity status). Subgroups can overlap and are often used in subgroup analyses.
Tunnel state	A temporary health state in a state transition (Markov) model used to capture time-dependent events or short-term effects that cannot be represented by standard Markov states.
Threshold analysis	An analysis used to identify the value of a key input at which an intervention becomes cost-effective.

List of appendices (separate documents)

Appendix A: Workshop notes

Appendix B: Health economic literature review

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