# Mount Hood 2025 Challenge 3

# (Obesity challenge)

## Motivation:

The impact of excess body weight on health and economic outcomes is well known, but the role of model uncertainty on cost-effectiveness estimates of interventions to reduce weight (such as lifestyle changes, pharmacological therapies, or surgical approaches) is less understood. The aim of Mt Hood 2025 Challenge 3 is to assess variability between obesity simulation models, in terms of estimated outcomes such as diabetes incidence, related complications, healthcare costs, and quality-adjusted life years (QALYs), over defined time horizons. It is expected that the results of this challenge will enhance our understanding of the predictive capabilities of different obesity simulation models, give insights into how the way costs and health utilities are applied, the choice of risk equations used, and model assumptions impact on short and long-term model projections. Overall, we aim to identify the best practices and areas for improvement in obesity simulation modelling.

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## Challenge 3: Estimating outcomes and cost-effectiveness of weightreducing interventions

**Objective:** To evaluate and compare the performance of different obesity simulation models in predicting the cardiovascular outcomes of overweight or obese patients without diabetes, based on the findings from the SELECT clinical trial.

**Background:** The SELECT clinical trial demonstrated that once-weekly subcutaneous semaglutide 2.4 mg significantly reduced the risk of major adverse cardiovascular events (MACE) by 20% compared to placebo in overweight or obese patients with established cardiovascular disease but without diabetes. The primary endpoint was the composite outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

This challenge is intended for simulation modelling groups with expertise in the areas of obesity, diabetes and cardiovascular disease. These groups will use their own obesity simulation model to predict outcomes based on the SELECT cardiovascular outcomes trial.

The challenge employs average baseline characteristics from the SELECT trial. Cost and utility inputs will either be explicitly provided for the Obesity Challenge or carried forward from the previous Challenge 1, as indicated below.

The average treatment effect of each category of intervention will be modelled by the reported mean changes from randomization to week 104 as reported in Table 3 of the primary SELECT trial paper (available here: <u>Semaglutide and Cardiovascular Outcomes in</u> <u>Obesity without Diabetes | New England Journal of Medicine</u>) (e.g. in body weight, glycated hemoglobin, systolic blood pressure, etc.). Parameter effects, for which effect evolution over time was reported (e.g., body weight or waist circumference as in Figure S6 of the supplementary material [available here: <u>NEJMoa2307563\_appendix.pdf</u>]) should be reproduced accordingly, if possible. Otherwise, if no effect time trends are reported, it should be assumed that the full effect establishes over a period of 52 weeks, assuming a linear effect evolution as a proxy.

The top-line methodological approaches to run the obesity modeling challenge are detailed below. Additional information can be found in the "Challenge simulation" section at the end of this document.

# Challenge 3A - Simulations comparing semaglutide 2.4 mg vs. placebo over a lifetime

### Base Case:

- Run simulations comparing semaglutide 2.4 mg vs. placebo over a lifetime (40-year) horizon.
- <u>Patient baseline characteristics</u>: Apply patient baseline characteristics from Table 2 (see below). If your model requires additional characteristics, please align as far as possible to baseline characteristics of as reported in Table S1 of the primary SELECT trial paper [available here: NEJMoa2307563 appendix.pdf].
- <u>Utilities:</u> Apply utility values as reported in the instructions for Challenge 1 instructions (Table 1 - Utility values by categories of diseases/complications; Type 2 diabetes section). Assume that decrements apply equally to the year of the event and to subsequent years. Utility values for obesity related complications should be applied from

Table 1. Utility values for obesity-related complications within the obesity challenge. All other utilities carry forward from Challenges 1 and 2

Complication	Mean	Standard Error	
Glycemic health state baseline utility			
Normoglycemia	0.948	0.190	
Pre-T2D	0.948	0.190	
T2D	0.785	0.157	
Cardiovascular disease (first year)			
Myocardial infarction (during year of event)	-0.063	0.003	
Unstable angina (or similar ischemic heart disease related complication considered in your model)	-0.063	0.003	
Stroke	-0.117	0.006	
TIA	-0.033	0.002	
Heart failure	-0.117	0.022	
Cardiovascular disease (subsequent years)			
Myocardial infarction (during year of event)	-0.037	0.007	
Unstable angina (or similar ischemic heart disease related complication considered in your model)	-0.037	0.007	
Stroke	-0.035	0.007	
TIA	-0.033	0.007	
Heart failure	-0.108	0.022	
Obesity related complications (first year)			
BaS	-0.184	0.009	
Osteoarthritis	-0.064	0.000	
Knee surgery post knee osteoarthritis	-0.064	0.003	
OSA	-0.038	0.002	
Asthma	-0.021	0.000	
Obesity related complications (subsequent years)			
BaS	-0.00	0.00	
Osteoarthritis	-0.064	0.000	
Knee surgery	-0.00	0.00	
OSA	-0.038	0.002	
Asthma	-0.021	0.000	
Disutility per unit BMI gained above 25 Kg/m2	0.0062	0.001	
Disutility for chronic kidney disease stages (first and subsequent years)			

CKD stage 2	-0.000	0.000
CKD stage 3a	-0.030	0.006
CKD stage 3b	-0.030	0.006
CKD stage 4	-0.050	0.010
CKD stage 5	-0.050	0.010
Abbreviations: BaS, bariatric surgery; BMI, body mass index; CKD, chronic kidney disease; OSA, obstructive sleep apnea; T2D, type 2 diabetes		

- of Challenge 3 (see below).
- <u>Healthcare costs</u>: Apply healthcare costs as reported in Challenge 1 instructions (Table 9. Complication costs (£, 2022–23)) and supplement costs for obesity related complications from Table 3 of Challenge 3 (see below).
- Intervention costs: Apply annual intervention costs from Table 4 (see below).
- Intervention effects: The average treatment effect of each category of intervention should be modelled by the reported mean changes from randomization to week 104 as reported in Table 3 of the primary SELECT trial paper (available here: Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes | New England Journal of Medicine). Parameter effects, for which effect evolution over time was reported (e.g., body weight or waist circumference as in Figure S6 of the supplementary material) should be reproduced accordingly, if possible. Please ensure the BMI trend corresponds to the body weight trend, assuming an average height of 170 cm. Otherwise, for parameters where no effect time trends are reported, it should be assumed that the full effect establishes over a period of 52 weeks, assuming a linear effect evolution as a proxy.
- Assume that patients remain on treatment for two years and then discontinue (with no treatment discontinuation within the first two years).
- Post-treatment discontinuation:
  - assume linear weight regain back to the previous baseline level over 3 years.
  - assume an immediate loss of effect for all other parameters that are affected by interventions.
  - expose patient risk factors to their natural progression trends as defined in your model.
- Set discounting for costs and health benefits to zero.
- If weight (kg) to BMI (kg/m<sup>2</sup>) conversion is required, assume an average height of 170 cm.

- If your model considers CKD stage progression alongside renal function decline, assume annual eGFR decline as follows:
  - Semaglutide 2.4 mg: -0.77 mL/min/1.73m<sup>2</sup> decline per year
  - Placebo (or post-treatment discontinuation): -1.40 mL/min/1.73m<sup>2</sup> decline per year
- If bariatric surgery is included in your model, apply the following assumptions:
  - Bariatric surgery incidence of 1.15% per year
  - Bariatric surgery eligibility threshold of BMI 35 kg/m<sup>2</sup>
- Run the model with 1,000 patients over a 40-year time horizon with a % discount rate and 1,000 internal loops. Note that we define internal loops (or Monte-Carlo trials) as the number of times the same patient is simulated through the risk equations to reduce first order uncertainty (Monte-Carlo error).
- More detailed information on how to run the base case analyses can be found in section 'Challenge simulation-Step 1 (base case)'.

#### Scenario analyses:

Please repeat the above simulation by altering the inputs as below, reporting the impact of each change on outcomes:

- Assume linear weight regain back to the previous baseline level over **1-year** post-treatment discontinuation (**SA1**).
- Repeat the base case and SA, assuming that patients remain on treatment for <u>5</u> years (SA2 and SA3).
- Assume that patients remain on treatment over a lifetime (SA4).

In summary, next to the base case analysis described above, this should add four additional simulations as detailed below:

	Time horizon	Therapy duration (years)	Effect reversal (years)
Base case	40	2	3
SA 1	40	2	1
SA 2	40	5	3
SA 3	40	5	1
SA 4	40	40	N/A

More detailed information on how to run scenario analyses can be found in section 'Challenge simulation-Step 2 (scenario analysis)'.

#### Challenge 3B - Conduct external validation against SELECT trial outcomes

Each group will use their model to conduct external validation against the reported SELECT trial outcomes

- Groups will repeat the base case simulation from challenge 3A with time horizon set to 4 years (please run 3 and 4 year simulations when your model does not allow extraction of time specific event counts) and the below modifications:
- The number of patients included in the modelling will be set to 8,803 and 8,801 in intervention and control treatment arms, respectively, to reflect the population size in both arms of the SELECT trial. For cohort models, please ensure that model outcomes are extrapolated to match expected outcomes in 8,802 patients.
- Assume that patients remain on treatment for the complete time horizon (no discontinuation)
- Apply intervention effects as detailed in Challenge 3A (based on reported mean changes from randomization to week 104 as reported in Table 3 of the SELECT paper and effect evolution for weight, BMI and/or waist circumference aligned to Figure S6)
- Keep all other inputs and configurations as in the base case scenario
- Collect the total number of predicted events for MACE (major adverse cardiovascular events), type 2 diabetes (T2D) onset, cardiovascular (CV) death, all-cause mortality, nonfatal myocardial infarction (MI), nonfatal stroke, heart failure and unstable angina.
- Report time specific (annual) outcomes from the 4-year projections. Outcomes for year 3 and year 4 will be interpolated automatically in the 'Challenge 3B results' tab to estimate expected events at the mean SELECT trial follow-up of 39.8 months (3.32 years).
- Please input results into "Results-CH 3B' section of the Excel result summary document. The document provides additional information on the required format of outcome reporting.
- Run the model with a % discount rate and 1,000 internal loops. Note that we
  define internal loops (or Monte-Carlo trials) as the number of times the same
  patient is simulated through the risk equations to reduce first order uncertainty
  (Monte-Carlo error).

• More detailed information on Challenge 3B can be found in section 'Challenge simulation-Step 3 (external validation)'.

# Model Inputs:

# Utility Values

Baseline utilities and disutilities for challenge 3 are presented in

Table 1. Any other required utility for complications that are considered in your model butnot reported in Table 1 may be obtained from utility inputs applied in Challenge 1(reference simulation). Please make sure to avoid confusion with utility/disutilityterminology in loading the models and in reporting results. Items with negative values aredisutilities and are incremental.

If possible, please set utility weights to zero for any health states where utilities are not reported either in **Error! Reference source not found.** or in the previous Challenge 1. If this is not possible, and you require real utility weights for additional health states not listed (e.g. a raised BMI health state which is independent of BMI's effect on complication events), please add utility values you currently use. Please document your sources and assumptions in the "Utility values" tab in the accompanying Excel spreadsheet.

Please also keep baseline utilities constant across all ages. Where possible, please do not change baseline utilities by age. However, if your model requires you to do so – please report this in the Excel sheet.

Based on the 2018 Mt. Hood challenge conference call on September 5, 2018, one suggestion was made for the Quality of Life challenge and which remains relevant for the current challenge, including:

The additive quality-of-life (QoL) model is recommended when populating the health utility values into the simulation model. If a subject has experienced two different complications belonging to two different disease categories of disease (e.g., stroke [in the category of cerebrovascular disease] and myocardial infarction [in the category of coronary heart disease]), the health utility value will be reduced by 0.219 which is the sum of individual decrements for these complications (0.164 + 0.055). However, if a subject has experienced two or more complications within the same disease category (e.g., myocardial infarction [in the category of coronary heart disease] and congestive heart failure [in the category of coronary heart disease] and congestive heart failure [in the category of coronary heart disease]), the health utility value will be reduced by 0.108, the decrement for heart failure, which is the largest decrement of these two complications. If the additive QoL model is not feasible in your model, please document your assumptions how the health utility values are populated in your model.

Table 1. Utility values for obesity-related complications within the obesity challenge. All other utilities carry forward from Challenges 1 and 2

Complication	Mean	Standard Error	
Glycemic health state baseline utility			
Normoglycemia	0.948	0.190	
Pre-T2D	0.948	0.190	
T2D	0.785	0.157	
Cardiovascular disease (first year)			
Myocardial infarction (during year of event)	-0.063	0.003	
Unstable angina (or similar ischemic heart disease related complication considered in your model)	-0.063	0.003	
Stroke	-0.117	0.006	
ΤΙΑ	-0.033	0.002	
Heart failure	-0.117	0.022	
Cardiovascular disease (subsequent years)			
Myocardial infarction (during year of event)	-0.037	0.007	
Unstable angina (or similar ischemic heart disease related complication considered in your model)	-0.037	0.007	
Stroke	-0.035	0.007	
TIA	-0.033	0.007	
Heart failure	-0.108	0.022	
Obesity related complications (first year)			
BaS	-0.184	0.009	
Osteoarthritis	-0.064	0.000	
Knee surgery post knee osteoarthritis	-0.064	0.003	
OSA	-0.038	0.002	
Asthma	-0.021	0.000	
Obesity related complications (subsequent years)			
BaS	-0.00	0.00	
Osteoarthritis	-0.064	0.000	
Knee surgery	-0.00	0.00	
OSA	-0.038	0.002	
Asthma	-0.021	0.000	
Disutility per unit BMI gained above 25 Kg/m2	0.0062	0.001	
Disutility for chronic kidney disease stages (first and subsequent years)			

CKD stage 2	-0.000	0.000
CKD stage 3a	-0.030	0.006
CKD stage 3b	-0.030	0.006
CKD stage 4	-0.050	0.010
CKD stage 5	-0.050	0.010
Abbreviations: BaS, bariatric surgery; BMI, body mass index; CKD, chronic kidney disease; OSA, obstructive sleep apnea; T2D, type 2 diabetes		

Source: Data on file

Os represent that no utility value has been sourced for these parameters. Where possible, please set these (and any additional) events to have zero impact on calculated utility to maintain comparability between model results. If it is not possible to use zero value, please document your default utility assumption in the Excel submission file.

#### **Patient Baseline Characteristics**

To allow for consistent comparisons across all models, baseline patient characteristics should follow the values listed in Table 2 below. Full baseline characteristics for the SELECT trial population are available in Table 1 of the primary SELECT trial results publication (available here: <u>Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes</u> | <u>New England Journal of Medicine</u>) and in Table S1 of the related supplementary appendix (available here: <u>NEJMoa2307563 appendix.pdf</u>).

If your model can accommodate additional characteristics from the trial publication, please include all possible characteristics and document this in the "Baseline Characteristics" tab in the accompanying Excel spreadsheet. Any other baseline patient characteristics that your model may require can be sourced from publicly available literature (but please document this including sources in in the "Baseline Characteristics" tab in the accompanying Excel spreadsheet).

If there are any characteristics noted that your model is unable to accommodate, please also document this in the "Baseline Characteristics" tab in the accompanying Excel spreadsheet

#### Table 2. Patient Baseline Characteristics

	Mean	SD
Demographics		
Age	61,6	8,9
Male –%	72,2	
Race or ethnic group (0 to 1)		
White	0,839	0,0839
Asian	0,082	0,0082
Black or African American	0,04	0,004
Other	0,029	0,0029
Hispanic or Latino	0,104	0,0104
Physical health risk determinants		
Body weight (kg)	96,5	17,5
Waist circumference (cm)	111,3	13,1
BMI – kg/m2	33,3	5
HbA1c	5,78	0,34
Distribution of glycemic states (%)		
< 5.7% (normoglycemic)	33,2	
≥ 5.7% (pre-diabetic)	66,8	
Median high-sensitivity C-reactive protein	1,87	0,84
eGFR – mean mL/min/1,73 m2	82,4	17,5
UACR – mg/g – median	7,4	2,86
Lipids – mg/dL		

Total cholesterol	153	13,01
HDL cholesterol	44	3,83
LDL cholesterol	78	10,46
Triglycerides	134	22,70
Systolic blood pressure – mmHg	131	15,6
Diastolic blood pressure – mmHg	79,4	10
Pulse – bpm	68,9	10,6
History of CVD (0 to 1)		
Unstable angina	0,058	0,0058
MI	0,764	0,0764
Coronary revascularization	0,674	0,0674
Stroke	0,234	0,0234
Symptomatic PAD	0,086	0,0086
Chronic heart failure	0,245	0,0245
Hypertension	0,819	0,0819
CV medications (0 to 1)	%	
Platelet aggregation inhibitors	0,865	0,0865
Acetylsalicylic acid	0,785	0,0785
P2Y12 receptor inhibitors	0,332	0,0332
Other	0,009	0,0009
Anti-thrombotic medications	0,123	0,0123
Vitamin K antagonists	0,038	0,0038
Direct oral anticoagulants	0,084	0,0084
Lipid-lowering drugs	0,901	0,0901
Statins	0,877	0,0877
Ezetimibe	0,135	0,0135
Fibrates	0,024	0,0024
PCSK-9 inhibitors	0,02	0,002
Beta blockers	0,702	0,0702
Angiotensin-converting-enzyme		
inhibitors	0,45	0,045
Angiotensin-receptor blockers	0,297	0,0297
Calcium channel blockers	0,273	0,0273
Source: Lincoff et al. N Engl J Med, 2023;389:2221-22	32	

#### Costs

Please apply the same set of complication costs as used in Challenges 1 and 2, in combination with costs for obesity related complications as provided in **Error! Reference source not found.** Intervention costs to be applied in this challenge are set as zero as given in **Error! Reference source not found.** 

As far as possible, please apply costs only to complication events described in the instructions for this and the previous challenges (1 and 2). As an example, if your model usually incorporates increased costs from raised BMI independently of complication events which occur, please turn this off if possible. If it is not possible to model costs only for complication events, then please report any additional costs separately.

Additionally, please set the baseline costs in the absence of complications to zero for the obesity challenge (challenge 3). Where possible, please use zero values for all additional cost elements your model may include beyond those listed in Table 3 and in the previous challenges. However, if your model does not permit this, please report values used in the Excel spreadsheet.

				Costs in
Cost Category	Event	Fatal costs (£)	Non fatal costs (£)	subsequent years (£)
Cardiovascular	Ischemic heart	(~)	00010 (2)	years (2)
disease	disease/Angina	7087	16348	4145
	Myocardial infarction	3874	11113	3998
	Heart failure	3298	6597	4994
	Stroke	7546	12558	4126
	TIA	0	2155	1338
	Coronary revascularisation	0	9693	4145
Obesity				
related	BaS	6250	6359	0
complications		6359		0
	Osteoarthritis	0	1029	1029
	Knee surgery	6492	6492	0
	OSA	0	1018	1234
	Asthma	0	1252	1252
Chronic kidney				
disease	CKD stage 2	0	203,27	203,27
	CKD stage 3a	0	1699,32	1699,32
	CKD stage 3b	0	1699,32	1699,32
	CKD stage 4	0	3927,96	3927,96
	CKD stage 5	0	6199,29	6199,29
	Peripheral vascular			
Other	disease	0	5485	1179
	Renal failure / transplant	12014	24027	24027
	Peritoneal Dialysis	(	38013	38013

#### Table 3. Supplementary health care cost inputs for the obesity challenge

Os represent that no cost value has been sourced for these parameters. Please set these (and any additional) events to have zero impact on calculated costs where possible to maintain comparability between model results. If not possible to use zero value, please document your default cost assumption in the Excel submission file

Table 4. Intervention costs

	Semaglutide 2.4 mg	Placebo
Annual costs	£0	£0

#### **Challenge simulation**

#### Step 1 (base case)

Run a simulation using the baseline characteristics from the SELECT trial over a 40-year time horizon based on specifications for the base case analysis as detailed above (see – Challenge 3A - Base Case).

Simulated patients in semaglutide and placebo arm should receive effects as detailed in Table 3 of the primary SELECT manuscript. Post treatment discontinuation, patients should follow natural risk factor progression trends. Discontinuation rules for semaglutide and placebo should be equally applied. If modeling groups can modify natural progression trends, it is preferred that blood pressure and lipid values remain constant over the remaining time horizon. Risk factor trends for BMI and HbA1c should be predicted as defined in your model. eGFR should decline at a rate of -1.40 mL/min/1.73m<sup>2</sup> decline per year in the placebo arm (or post-treatment discontinuation). Simulated patients receiving semaglutide 2.4 mg should be modelled to experience an eGFR decline of -0.77 mL/min/1.73m<sup>2</sup> decline per year.

Please ensure that costs and health outcomes are not discounted for this challenge.

Extract the results and enter values in a transparent manner in the accompanying Excel workbook in tab labelled "Time paths & Outc.-CH 3A" (modify the workbook to fit your outcomes if necessary, adding any which you feel are relevant, but please try to preserve the basic structure). Do not forget to include traces (risk factor time paths) for input values of all relevant risk factors (most importantly, BMI or weight); cumulative events over time for all major events in the model (e.g. MI; stroke; HF, etc.). Please also document life-expectancy, QALE and total healthcare costs observed over the 40 year time horizon.

Run the simulation including 1,000 patients and 1,000 internal loops to remove Monte Carlo error (random noise).

A summary of the outcomes to be reported in tab labelled "Time paths & Outc.-CH 3A" are listed below:

Risk factor time paths

- o BMI (Kg/m2)
- o HbA1c (%)
- Total Cholesterol (mg/dl)
- HDL (mg/dl)
- LDL (mg/dl)
- SBP (mm Hg)
- o DBP (mm Hg)
- o eGFR
- Heart rate
- Cumulative events over time
  - o MACE
  - o Non fatal MI (including primary and recurrent events)
  - o Fatal MI (including primary and recurrent events)
  - Non fatal Stroke (including primary and recurrent events)
  - Fatal Stroke (including primary and recurrent events)
  - Unstable angina (f & nf) (including primary and recurrent events)
  - Heart Failure (f & nf) (including primary and recurrent events)
  - $\circ \quad \text{CV death} \\$
  - $\circ \quad \text{All cause death} \\$
  - Onset of type 2 diabetes
  - o Osteoarthritis
  - o Knee surgery
  - o Bariatric surgery
  - o Asthma
  - Cancers (add total sum if your model considers different kinds of cancers)
- Lifetime outcomes (please report outcomes at 40 years)
  - o Total life expectancy
  - o Total QALE
  - o Total healthcare costs

Please be aware that no outcomes should be entered in the 'Results-CH 3A' tab, as it serves as a summary of the reported outcomes in the 'Time paths & Outc.-CH 3A' tab. However, the 'Results-CH 3A' tab can be used for quality control to verify that the reported outcomes are reasonable and align with your modeling results. Additionally, please ensure that any questions posted in this tab are answered..

#### Step 2 (scenario analysis)

Complete four additional simulations (SA 1 to SA 4, shown below) by rerunning your model base-case but altering the time period of linear weight regain post-treatment discontinuation, and the time period patients remain on treatment:

	Time horizon	Therapy duration (years)	Effect reversal (years)
Base case	40	2	3
SA 1	40	2	1
SA 2	40	5	3
SA 3	40	5	1
SA 4	40	40	N/A

Extract the results of these analyses (as detailed above) into the appropriate cells within the tab 'Time paths & Outc.-CH 3A'.

#### Step 3 (external validation)

Using the same inputs and configurations as applied in the base case analysis (Obesity Challenge 3A), conduct additional simulations with of 4 year time horizons to replicate the SELECT trial scenario. Please run 3 and 4 year simulations when your model does not allow extraction of time specific event counts to facilitate subsequent interpolation to the median trial follow-up of 3.32 years. Please apply the following assumptions:

- Please run separate simulations for patient baseline characteristics in semaglutide 2.4 mg and placebo arms. While baseline characteristics for slemaglutide 2.4 mg are provided in Table 2 of this document, baseline characteristics for the placebo arm can be obtained from 'Table S1. Expanded Baseline Characteristics of the Patients' from the SELECT trial publication (<u>NEJMoa2307563 appendix.pdf</u>).
- Please include 8,803 and 8,801 patients in semaglutide and placebo arms, respectively, to replicate the size of the SELECT trial population (please note, the correct reflection of population size is crucial for the validation exercise since total event counts from model predictions and trial observations are compared).
- Apply average treatment effects as reported in Table 3 of the primary SELECT trial paper (available here: <u>Semaglutide and Cardiovascular Outcomes in Obesity</u> without Diabetes | New England Journal of Medicine).
- Body weight, BMI and/or waist circumference (parameters for which effect evolution over time is in Figure S6 of the supplementary material) should be reproduced accordingly, if possible. Please ensure the BMI trend corresponds to the body weight trend, assuming an average height of 170 cm.
- For parameters where no effect time trends are reported, it should be assumed that the full effect establishes over a period of 52 weeks, assuming a linear effect evolution as a proxy. No change of parameter level should be assumed beyond 52 weeks.

- Assume that patients remain on treatment for the complete time horizon (4 years).
- Collect the total number of predicted events for MACE, T2D onset, CVD-death, allcause mortality, nonfatal MI, nonfatal stroke heart failure and unstable angina and evaluate the cumulative event count over time.
- Extract the results and enter values in a transparent manner in the accompanying Excel workbook in tab labelled "Time paths & Outc.-CH 3B".
- No outcomes should be entered in the 'Results-CH 3B' tab, as it presents the 3.32year <u>time interpolated</u> outcomes from the 3-year and 4-year. You may use the 'Results-CH 3B' tab to intercompare your model predictions to observed trial outcomes (Table 2 of the SELECT paper). Additionally, please ensure that any questions posted in this tab are answered.
- Please apply 1,000 internal loops. Note that we define internal loops (or Monte-Carlo trials) as the number of times the same patient is simulated through the risk equations to reduce first order uncertainty (Monte-Carlo error).
- Set discounting to 0%.

Note: modelling groups only need to present the 3- and 4-year projected outcomes. Interpolated results are generated automatically.

Note: it is anticipated that there may be discrepancies in the prediction of mortality as a result of the SELECT trial population having lower mortality rate than that of an agematched general population cohort.

#### **Summary of findings:**

Compile a summary of your findings in the accompanying Excel spreadsheet (in tab labelled "Summary"). Please complete the following.

- A) Comment on the accuracy of your predicted cardiovascular outcomes and diabetes incidence compared to actual trial results (reported here: <u>Semaglutide and</u> <u>Cardiovascular Outcomes in Obesity without Diabetes | New England Journal of</u> <u>Medicine</u>).
- B) Comment on the consistency of your risk reduction estimates with the SELECT trial findings.
- C) Provide an overview of what you learnt from this challenge.

#### Submission:

Prior to the meeting, please submit the Excel spreadsheet ("MtHood\_Obesity\_Challenge\_2025\_Results v1.0.xlsx") to Mount Hood at: <u>mthood2016@gmail.com</u> by XX<sup>th</sup> of XXX. Please replace GROUP with your modelling group name before submission.

**Commented [GR1]:** Placeholder - Mount Hood team, please advise and update