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Oral Semaglutide for Type 2 Diabetes: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes mellitus (T2DM). Elements of this model analysis plan are subject to change as the project progresses. Refer to the research protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the lifetime cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for T2DM using a decision analytic model. Oral semaglutide added to current antihyperglycemic treatment will be separately compared to four modeled comparators including: (1) ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas), (2) sitagliptin, (3) empagliflozin, and (4) liraglutide; comparators (2), (3), and (4) are also added to current antihyperglycemic treatment. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime horizon. Productivity impacts and other indirect costs will be considered in a scenario analysis using a societal perspective, if data allow. The model will be developed in Microsoft® Excel® for Office 365 (Version 1906).

2. Methods

2.1 Overview and Model Structure

We will develop an adaptation of a published microsimulation model[1] based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2 (OM2) [2] for this evaluation, informed by the PIONEER clinical trials,[3-10] relevant quality of life literature, and validation versus other prior economic models.[11-15] The base case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year.[16]

The model (Figure 2.1) will be an individual patient-level, Monte Carlo-based microsimulation of costs, quality of life, clinical events, and mortality associated with T2DM among United States (US) adults with the disease. Three modeling steps will be used: (1) individual patient simulation; (2) event microsimulation; and (3) calculation of mean results from the pool of simulated patients' lifetime outcomes. Simulated patients will be run through the modeling steps for each comparator versus oral semaglutide added to current ongoing background antihyperglycemic treatment. The three model steps are explained below:

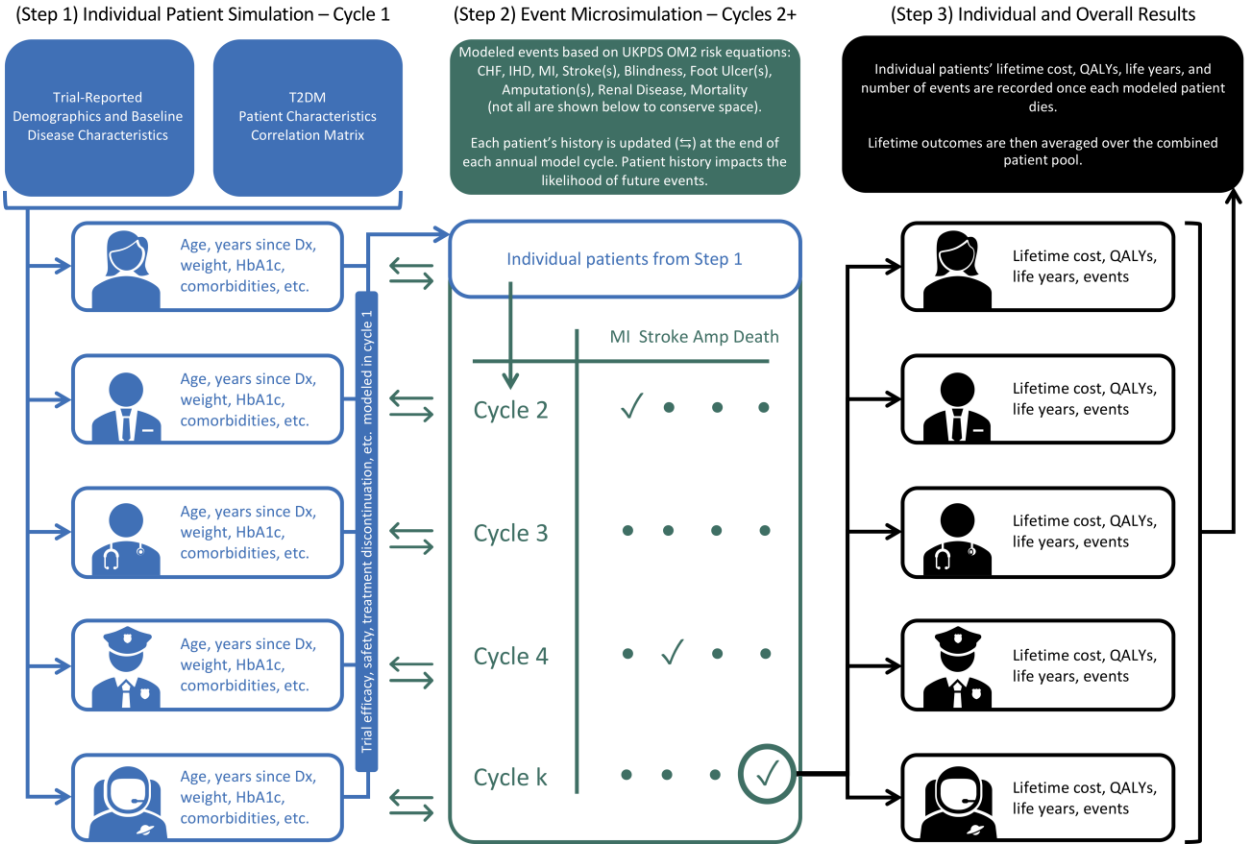
(1) Individual patient simulation. Individual patients based on NHANES patient demographics will be computer-generated using Monte Carlo simulation. All relevant and available mean and

standard deviation values for each patient characteristic will be utilized for the patient simulation. In recognition that disease characteristics (e.g., time since diagnosis, glycated hemoglobin [HbA1c], body weight, estimated glomerular filtration rate, etc.) are correlated with each other, we will use a correlation matrix (see Appendix) of disease characteristics derived from Veterans Affairs data on T2DM patients to draw correlated Monte Carlo values for each characteristic. After simulating the baseline population, we will then use the results from a network meta-analysis (NMA) of cardiovascular and renal outcomes, as well as trial outcomes for changes in HbA1c and body mass index (BMI), to replicate the results of the PIONEER trials within the first year.

(2) Event microsimulation. Each simulated patient from step 1 will then be sequentially run through the event microsimulation. Each model cycle will be one year in duration. The UKPDS OM2 risk equations, plus a module for hypoglycemia, will be used along with hazard ratios from the NMA of cardiovascular and renal outcomes to calculate the incidence of a clinical event and/or mortality in each year until the simulated patient dies. All event and/or mortality associated costs and health state utility weights will be applied concurrently. The UKPDS OM2 risk equations account for patient history upon entering the model as well as new clinical events that occur during the microsimulation; for example, a patient who experiences a first myocardial infarction (MI) in a given year of the microsimulation is no longer at risk for a first MI, but becomes eligible for the previously inactive risk equation for a subsequent MI in each subsequent year.

(3) Calculation of mean results. After each simulated patient dies, the model will record the patient's lifetime cost, QALYs, life years, and clinical events. Each outcome is then averaged over the entire pool of simulated patients to derive overall model results.

Figure 2.1. Model Schematic



T2DM = type 2 diabetes mellitus; Dx = diagnosis; HbA1c = glycated hemoglobin; CHF = congestive heart failure; IHD = ischemic heart disease; MI = myocardial infarction; Amp = amputation; QALY = quality-adjusted life year

2.2 Key Model Choices and Assumptions

Below is a list of key model choices:

- Long-term survival and the incidence of diabetes-related clinical events will be modeled using an adaptation of the UKPDS OM2 risk equations.[1,2]
- The model will utilize hazard ratios derived from the NMA using the results of PIONEER 6 and comparator cardiovascular outcome trials (CVOTs)[5,17-19] for cardiovascular and renal disease outcomes.
- Survival will be weighted by disutilities for each diabetes-related complication to model quality of life.[20] If available, we will also employ disutilities for individual adverse events.
- The model will include all treatment costs associated with each individual drug regimen, including drug acquisition costs and supportive care costs (e.g., clinician visits and self-monitoring).
- All model outcomes will be calculated over a lifetime time horizon.[16]

- Life-years, QALYs, and health care cost outcomes will be discounted at 3% per year. [16]

Our model includes several assumptions stated below.

Table 2.1. Key Model Assumptions

Assumption	Rationale
HbA1c remains stable after end of trial and throughout patient lifetime for patients who remain on treatment.	Long-term effectiveness is currently unknown. We will model changes in long-term HbA1c in scenario analyses.
Weight/BMI remains stable after end of trial and throughout lifetime for patients who remain on treatment.	Long-term effectiveness is currently unknown. We will model changes in long-term BMI in scenario analyses.
The incremental rate of kidney function decline and major adverse cardiovascular events (MACE) is independent of HbA1c control.	Contemporary clinical trials have demonstrated an independent relationship between changes in HbA1c and both renal failure and MACE.
Calibration of UKPDS OM2 for CV and renal outcomes, based on NMA results, will be maintained over patient lifetime.	Long-term effectiveness is currently unknown. We will potentially model relative changes in long-term CV and renal outcome effectiveness in scenario analyses.
Ongoing background antihyperglycemic medications are assumed the same for all comparators.	The goal is to evaluate direct comparisons among the treatments of interest and not multiple possible treatment sequences.

2.3 Populations

The population of interest for this review is adults with T2DM with inadequate glycemic control despite current treatment with antihyperglycemic agent(s). A cohort of individual patients will be simulated based on the characteristics of U.S. adults aged ≥30 years with self-reported diabetes from NHANES (Table 2.2). Simulated patients will be drawn from a population with 50% females and a mean age of 61 years, with a mean of 9.7 years since diagnosis of T2DM. These patients will be distributed with a mean HbA1c of 7.4% and BMI of 32.8 kg/m^2.

Table 2.2. Characteristics of US Adults Aged ≥30 Years with Self-Reported Diabetes, NHANES 2011–2012[1]

Characteristic	Weighted Mean (SD)	Percentage (95% CI)
Age, y	61.0 (0.6)	-
30–44 y	-	9 (6–13)
45–64 y	-	48 (44–52)
65–75 y	-	26 (21–31)
75 y	-	17 (14–19)
Female	-	50 (45–55)
Black/African American	-	17 (8–25)
HbA1c level, *%*	7.4 (0.1)	-
Duration of diabetes, *y*	9.7 (0.4)	-
Duration of diabetes <10 y	-	44 (38–50)
Current smoker	-	17 (13–21)
Body mass index, *kg/m²*	32.8 (0.5)	-
Low-density lipoprotein cholesterol level, *mg/dL*	46.8 (1.8)	
High-density lipoprotein cholesterol level, *mg/dL*	21.6 (5.4)	-
Hemoglobin level, *g/dL*	13.7 (0.01)	-
Leukocyte count, *× 1000 cells/µL*	7.5 (0.1)	-
Heart rate, *beats/min*	73.4 (1.0)	-
Systolic blood pressure, *mm Hg*	129.9 (0.9)	-
Estimated glomerular filtration rate, *mL/min/1.73 m²*	78.8 (1.1)	-
Albuminuria	-	19 (13–24)
History of diabetic complications	-	36 (30–42)
Macrovascular events	-	28 (23–33)
Microvascular events	-	14 (10–18)
Background medication	-	
Metformin	-	51 (42–60)
Sulfonylurea	-	33 (25–42)

CI: confidence interval, HbA1c: glycated hemoglobin, kg: kilogram, m: meter, mg/dL: milligram per deciliter, min: minute, SD: standard deviation, y: year, µL: microliter

2.4 Interventions

Our intervention of interest for this review is oral semaglutide (Novo Nordisk) added to current ongoing background antihyperglycemic treatment.

Comparators

We plan to compare to each of the following treatments:

- Ongoing background antihyperglycemic treatment (e.g., metformin with or without sulfonylureas) alone
- Sitagliptin (Januvia®, Merck), a DPP-4 inhibitor, added to ongoing background treatment
- Empagliflozin (Jardiance®, Boehringer Ingelheim and Eli Lilly), a SGLT-2 inhibitor, added to ongoing background treatment

- Liraglutide (Victoza®, Novo Nordisk), an injectable GLP-1 receptor agonist, added to ongoing background treatment

The three add-on agents were chosen in part because they were active comparators in the trials of oral semaglutide.

2.5 Input Parameters

Clinical Inputs

Clinical inputs regarding the efficacy of oral semaglutide compared to ongoing background antihyperglycemic treatment, sitagliptin, empagliflozin, and liraglutide on intermediate outcomes such as HbA1c and body weight will be derived from the head-to-head PIONEER trials[3,4,7,8]. We will perform a NMA of PIONEER 6 and the comparator CVOTs[5,17-19] to obtain hazard ratios for each comparator versus oral semaglutide for MACE, CHF, and renal failure outcomes, as well as corresponding baseline rates for oral semaglutide; hazard ratios will be applied to the oral semaglutide baseline rate to derive the outcome rates for ongoing background antihyperglycemic treatment, sitagliptin, empagliflozin, and liraglutide. In the absence of data for oral semaglutide on key measures of benefit, we will use data from the injectable semaglutide CVOT.[21]

Diabetes-Related Complication and Mortality Probabilities

We will model diabetes-related complications and mortality based on risk equations from the UKPDS OM2.[2] The UKPDS OM2 risk equations are widely used in diabetes simulation models, and have been shown to accurately predict results for the population in which it was developed as well as other diabetes populations.[2,22-24]

The UKPDS OM2 complications (13 risk equations) include congestive heart failure (CHF), ischemic heart disease (IHD), first MI for females, first MI for males, subsequent MI, first stroke, subsequent stroke, blindness, foot ulcer, first amputation without prior ulcer, first amputation with prior ulcer, subsequent amputation, and end stage renal disease (ESRD).[2] Patients will be able to experience multiple and concurrent complications during each modeled year.

We will also add a hypoglycemia module to model the associations of T2DM medications with an increased annual risk for mild or moderate and severe hypoglycemia events.[25] The rates of hypoglycemia for each medication are under review. We plan to utilize the previous approach from Laiteerapong et al., wherein patients were at risk for a mild/moderate or severe hypoglycemic event depending on treatment, and were assumed to have no more than 1 mild/moderate and 1 severe hypoglycemic event per year during their lifetime.[1] Also from Laiteerapong et al. (from Ginde et al.), we will assume that a severe hypoglycemic event will result in physician visits 96.5% of

the time, emergency department visits 2.6% of the time, and hospitalizations 0.9% of the time, with different costs (see below) for each.[1,26]

Discontinuation Due to Adverse Events

We will apply pooled estimates of treatment discontinuation due to adverse events, along with assumptions for long-term treatment discontinuation, as applicable for oral semaglutide and each comparator. Patients discontinuing their primary modeled treatment will be assumed to transition to insulin therapy. This choice was made in order to be able to evaluate the four medications head-to-head as opposed to evaluating differences in different medication treatment pathways. Therefore, all patients who discontinue will use the same treatment (insulin) for the remainder of the model time horizon. Insulin treatment costs will be modeled using mean doses from a literature review, applied to unit costs similar to the model comparators.[27] Clinical characteristics for patients on insulin will be modeled using equations for HbA1c and weight, which will then drive the event risk equations for those patients.[27]

Mortality

The UKPDS OM2 risk equations predict that previous T2DM-related complications (except foot ulcer and blindness) increase the probability of death. The four mortality risk equations include death without history of clinical event(s), death in the year of a clinical event, death in subsequent year of prior event(s), and death with history of clinical event(s).[2]

Health State Utilities

We will use consistent health state utility values across treatments evaluated in the model. Separate utilities will be used for the year in which a complication occurs and for patient history of each complication, if applicable. Health state utilities will be derived from publicly available literature and/or manufacturer-submitted data and applied to the modeled events. We plan to utilize estimates for T2DM complications primarily from Shao et al.,[20] plus estimates for foot ulcer and amputation events from a recent diabetes utility study by Sullivan and Ghushchyan.[28] In Shao et al., the Health Utilities Index Mark 3 (HUI-3) was used to measure heath utility in a sample of 8,713 patients from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of high cardiovascular disease risk T2DM patients.[29] Sullivan and Ghushchyan mapped EQ-5D-3L questionnaire responses to the Short Form-12 health survey responses of 20,705 individuals with diabetes (types 1 and 2) in the Medical Expenditure Panel Survey (MEPS) database from 2000 to 2011.[28] Lastly, we will model an annual disutility for daily injection of insulin (for patients who discontinue treatment) and liraglutide based on Boye et al., who used standard gamble interviews of T2DM patients in Scotland to estimate the utility values for injection-related attributes.[30]

Table 2.3. Health State Utilities/Disutilities

	Estimate	SE	Lower	Upper
Baseline Utility	0.800	0.023	0.755	0.845
Macrovascular complications				
Congestive heart failure event[20]	-0.089	0.022	-0.132	-0.047
Congestive heart failure history[20]	-0.041	0.010	-0.060	-0.022
Ischemic heart disease history*[20]	-0.016	0.005	-0.026	-0.006
Myocardial infarction event[20]	-0.042	0.016	-0.074	-0.010
Myocardial infarction history[20]	-0.011	0.006	-0.022	0.001
Stroke event[20]	-0.204	0.035	-0.272	-0.136
Stroke history[20]	-0.101	0.008	-0.117	-0.086
Microvascular complications				
Blindness history[20]	-0.057	0.009	-0.074	-0.040
Foot ulcer event[28]	-0.024	0.005	-0.033	-0.015
Amputation event[28]	-0.051	0.029	-0.108	0.005
Renal disease history[20]	-0.024	0.016	-0.056	0.008
Hypoglycemia event[20]	-0.036	0.010	-0.056	-0.016
Hypoglycemia history[20]	-0.033	0.011	-0.054	-0.011
Demographic characteristics[20]†				
Annual disutility of daily injection (liraglutide and insulin only)[30]	-0.054		-20%	+20%

SE: standard error

*Disutility for ischemic heart disease is based on "revascularization history" from Shao et al.[20]

†Refer to Shao et al. for full list of multivariate regression results by patient demographic.

Drug Utilization

The following inputs will be used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each add-on regimen
- Protocol dosage for the indication
- Treatment adherence (base case assumption = 100% since modeling treatment efficacy and safety based on randomized controlled trial data)

Table 2.4. Treatment Regimen Recommended Dosage

	Oral Semaglutide	Sitagliptin	Empagliflozin	Liraglutide
Brand Name		Januvia®	Jardiance®	Victoza®
Manufacturer	Novo Nordisk	Merck	Boehringer Ingelheim & Eli Lilly	Novo Nordisk
Route of Administration	oral	oral	oral	subcutaneous
Dosing	14 mg daily	25 mg , 50 mg, or 100 mg daily	10 mg or 25 mg daily	1.2 mg or 1.8 mg daily

Mg: milligram

Cost Inputs

Drug Costs

Because oral semaglutide is not approved by the FDA, the drug price is not yet available. If the drug cost or an analyst estimate is not available at the time of the report, we will use the price of injectable semaglutide as a placeholder price, as well as calculate the threshold prices at three willingness to pay (WTP) thresholds: $50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained. If the cost is available at the time of the report, we will apply estimated branded drug discount rates to obtain net pricing estimates.

For each comparator, we obtained net pricing estimates from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price.[31] We estimated net prices by comparing the most recent four-quarter averages (i.e., second quarter of 2018 through first quarter of 2019) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (accessed July 2019) to arrive at an estimated net price per unit.

Table 2.5. Drug Costs

Drug	WAC per 30-Pill Bottle/Pen	Net Price Per 30-Pill Bottle/Pen	Discount From WAC	Net Price per Year‡
Oral Semaglutide*	$386.21	$250.77	35%	$13,040.04
Sitagliptin (Januvia®)	$451.20	$123.62	72.6%	$1,505.07
Empagliflozin (Jardiance®)	$492.85	$171.51	65.2%	$2,088.13
Liraglutide (Victoza®)†	$307.26	$219.38	28.6%	$5,341.90
Metformin				$917.19[1]
Sulfonylureas				$578.54[1]

WAC: wholesale acquisition cost

*As a placeholder, we used Ozempic (injectable semaglutide) prices. The placeholder price is for 2 mg/1.5 ml per week

†Prices for liraglutide are per 3 ml pen, and the annual price calculation assumes a 1.2mg/day dosage.

‡1 year = 365.25 days or 52 weeks

Please refer to the ICER Reference Case for more details on drug pricing.

Non-Drug Costs

Costs for T2DM-related complications and hypoglycemia were obtained from Ward et al., who estimated direct medical costs from data sources including inpatient and emergency department databases, national physician and laboratory fee schedules, government reports, and published literature.[32] Complication costs in the year of the event reflect acute care and any subsequent care provided in the first year; history state costs reflect annual resource use for the ongoing management of complications in subsequent years.[32] Costs were assessed from the perspective of a comprehensive US healthcare payer and were originally reported in 2012 US dollars (USD); the costs in Table 2.6. reflect inflation according to the first half of 2019. Data permitting, other health care costs related to diabetes monitoring may be included in the model.

Table 2.6. Cost per T2DM-Related Complication and per Hypoglycemic Event

	Estimate	Lower (-20%)	Upper (+20%)
Incremental Cost in the Year of Event/Diagnosis (per event)[32,33]			
Heart Failure	$28,021	$22,417	$33,626
Ischemic Heart Disease	$25,247	$20,198	$30,297
Myocardial Infarction	$66,574	$53,259	$79,889
Stroke	$49,677	$39,742	$59,612
Foot Ulcer	$2,532	$2,026	$3,039
Amputation	$10,663	$8,531	$12,796
Hypoglycemia			
Episode Requiring Hospitalization	$19,435	$15,548	$23,322
Episode Requiring ED visit	$1,546	$1,237	$1,856
Episode Requiring Glucagon Injection	$208	$166	$249
Incremental Cost of Living with History of Complication (per year)[32,33]			
Heart Failure*	$2,246	$1,797	$2,695
Ischemic Heart Disease*	$2,246	$1,797	$2,695
Myocardial Infarction*	$2,246	$1,797	$2,695
Stroke	$18,329	$14,663	$21,994
Blindness	$3,376	$2,700	$4,051
Renal Disease	$84,583	$67,666	$101,499

*Annual state costs for cardiovascular complications were obtained from a Medical Expenditure Panel Survey report on heart condition-associated office visits and medications.

2.6 Model Outcomes

Model outcomes will include life years (LYs) gained as an estimate of equal value life years gained (evLYGs), QALYs gained, clinical events, cost per MACE avoided, and total costs for each intervention over a lifetime time horizon. Costs will also be reported by the clinical event in order to understand the contribution of different cost elements. All costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum.[16]

2.7 Model Analysis

Cost-effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing oral semaglutide to each comparator, from a health care sector perspective in the base case analyses. Additionally, we will present a cost per consequence outcomes including cost per MACE avoided and cost per renal disease avoided.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 1,000 simulations (or the minimum number necessary to achieve statistical convergence), then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Modified societal perspective that includes components such as productivity impacts or other indirect costs as applicable.
2) Modeled time horizon
3) Sub-groups from PIONEER trials
4) Alternative risk equations vs. the UKPDS OM2
5) Increased/decreased BMI and HbA1c over patient lifetime
6) Relative changes in long-term MACE and renal outcome effectiveness

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other T2DM cost-effectiveness models. The outputs from the model will be validated against the PIONEER trial data of the interventions and also any relevant observational datasets.

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APPENDICES

Appendix A. Inputs for Monte Carlo Simulation

Table A1. Patient Baseline Characteristics Correlation Matrix from Veterans Affairs Data*

	Age	Female	White	Black	BMI	Metformin	HbA1c	PVD	MI Hist	Stroke Hist	Hypertension	Valve Dis.	Amp Hist	Pulmonary	Paralysis	Other Neuro	Liver Dis.	Arthritis	Electrolyte Dis.	Blood Loss	Anemia	Alcohol Use	Drug Use	Psychiatric	Depression	LDL	SBP
Age	**1.000**	-0.092	0.182	-0.168	-0.311	-0.043	-0.167	0.104	0.062	0.111	0.099	0.091	-0.008	0.020	0.004	0.039	-0.051	0.023	0.034	0.028	0.093	-0.085	-0.101	-0.100	-0.063	-0.108	0.087
Female	-0.092	**1.000**	-0.026	0.044	0.050	0.033	-0.002	-0.020	-0.018	-0.013	-0.010	-0.006	0.001	-0.002	0.001	0.004	0.000	0.007	0.005	-0.001	0.003	-0.007	-0.002	0.038	0.021	0.042	-0.002
White	0.182	-0.026	**1.000**	-0.699	0.058	-0.010	-0.092	0.036	0.041	0.015	-0.004	0.040	0.007	0.007	-0.006	0.012	-0.023	0.017	0.013	0.004	0.007	-0.039	-0.066	-0.024	0.008	-0.077	-0.035
Black	-0.168	0.044	-0.699	**1.000**	-0.019	0.010	0.074	-0.022	-0.033	-0.003	0.012	-0.032	-0.003	0.000	0.014	-0.009	0.017	-0.013	-0.007	-0.002	0.003	0.044	0.083	0.022	-0.008	0.080	0.052
BMI	-0.311	0.050	0.058	-0.019	**1.000**	0.000	0.032	-0.067	-0.028	-0.077	-0.039	-0.032	-0.001	0.010	-0.022	-0.042	-0.007	-0.021	-0.037	-0.011	-0.062	-0.024	-0.019	0.011	0.005	0.009	0.060
Metformin	-0.043	0.033	-0.010	0.010	0.000	**1.000**	-0.128	-0.010	0.005	0.002	-0.037	-0.001	0.007	-0.005	-0.002	0.012	0.001	0.000	-0.001	0.003	-0.002	0.003	0.002	0.012	-0.003	0.034	-0.029
HbA1c	-0.167	-0.002	-0.092	0.074	0.032	-0.128	**1.000**	-0.014	-0.007	-0.018	-0.019	-0.018	0.004	-0.004	0.006	-0.008	0.012	-0.008	-0.003	-0.004	-0.028	0.026	0.033	0.017	0.020	0.112	0.040
PVD	0.104	-0.020	0.036	-0.022	-0.067	-0.010	-0.014	**1.000**	0.059	0.076	0.116	0.089	0.043	0.029	0.031	0.043	0.007	0.027	0.051	0.029	0.066	0.013	-0.003	0.001	0.032	-0.028	-0.009
MI Hist	0.062	-0.018	0.041	-0.033	-0.028	0.005	-0.007	0.059	**1.000**	0.086	0.067	0.062	0.008	0.017	0.018	0.024	0.002	0.016	0.040	0.011	0.042	-0.002	0.009	0.012	0.018	-0.056	-0.042
Stroke Hist	0.111	-0.013	0.015	-0.003	-0.077	0.002	-0.018	0.076	0.086	**1.000**	0.078	0.052	0.003	0.011	0.125	0.103	0.003	0.006	0.046	0.022	0.055	0.003	-0.002	0.016	0.029	-0.039	-0.006
Hypertension	0.099	-0.010	-0.004	0.012	-0.039	-0.037	-0.019	0.116	0.067	0.078	**1.000**	0.098	0.010	0.037	0.038	0.072	0.038	0.034	0.089	0.030	0.116	0.043	0.030	0.051	0.084	-0.051	0.047
Valve Dis.	0.091	-0.006	0.040	-0.032	-0.032	-0.001	-0.018	0.089	0.062	0.052	0.098	**1.000**	-0.001	0.064	0.026	0.035	0.008	0.016	0.065	0.033	0.067	-0.004	-0.005	0.000	0.012	-0.028	-0.014
Amp Hist	-0.008	0.001	0.007	-0.003	-0.001	0.007	0.004	0.043	0.008	0.003	0.010	-0.001	**1.000**	0.009	0.014	0.005	0.006	-0.001	0.004	0.006	0.008	0.003	0.004	0.005	0.004	-0.007	-0.004
Pulmonary	0.020	-0.002	0.007	0.000	0.010	-0.005	-0.004	0.029	0.017	0.011	0.037	0.064	0.009	**1.000**	0.022	0.027	0.014	0.008	0.030	0.014	0.035	-0.004	0.000	0.003	0.010	-0.014	-0.006
Paralysis	0.004	0.001	-0.006	0.014	-0.022	-0.002	0.006	0.031	0.018	0.125	0.038	0.026	0.014	0.022	**1.000**	0.072	0.011	0.006	0.041	0.012	0.029	0.012	0.001	0.015	0.028	0.000	-0.015
Other Neuro	0.039	0.004	0.012	-0.009	-0.042	0.012	-0.008	0.043	0.024	0.103	0.072	0.035	0.005	0.027	0.072	**1.000**	0.019	0.005	0.074	0.010	0.048	0.027	0.020	0.065	0.049	-0.010	-0.014
Liver Dis.	-0.051	0.000	-0.023	0.017	-0.007	0.001	0.012	0.007	0.002	0.003	0.038	0.008	0.006	0.014	0.011	0.019	**1.000**	0.013	0.032	0.023	0.029	0.080	0.074	0.030	0.030	-0.003	-0.010

Arthritis	0.023	0.007	0.017	-0.013	-0.021	0.000	-0.008	0.027	0.016	0.006	0.034	0.016	-0.001	0.008	0.006	0.005	0.013	**1.000**	0.014	0.001	0.034	-0.004	-0.003	0.002	0.012	-0.010	-0.007
Electrolyte Dis.	0.034	0.005	0.013	-0.007	-0.037	-0.001	-0.003	0.051	0.040	0.046	0.089	0.065	0.004	0.030	0.041	0.074	0.032	0.014	**1.000**	0.039	0.104	0.048	0.028	0.047	0.043	-0.013	-0.016
Blood Loss	0.028	-0.001	0.004	-0.002	-0.011	0.003	-0.004	0.029	0.011	0.022	0.030	0.033	0.006	0.014	0.012	0.010	0.023	0.001	0.039	**1.000**	0.099	0.010	0.001	-0.004	0.005	-0.007	-0.005
Anemia	0.093	0.003	0.007	0.003	-0.062	-0.002	-0.028	0.066	0.042	0.055	0.116	0.067	0.008	0.035	0.029	0.048	0.029	0.034	0.104	0.099	**1.000**	0.015	0.008	0.028	0.027	-0.044	-0.017
Alcohol Use	-0.085	-0.007	-0.039	0.044	-0.024	0.003	0.026	0.013	-0.002	0.003	0.043	-0.004	0.003	-0.004	0.012	0.027	0.080	-0.004	0.048	0.010	0.015	**1.000**	0.313	0.139	0.096	0.010	-0.017
Drug Use	-0.101	-0.002	-0.066	0.083	-0.019	0.002	0.033	-0.003	0.009	-0.002	0.030	-0.005	0.004	0.000	0.001	0.020	0.074	-0.003	0.028	0.001	0.008	0.313	**1.000**	0.147	0.079	0.016	-0.013
Psychiatric	-0.100	0.038	-0.024	0.022	0.011	0.012	0.017	0.001	0.012	0.016	0.051	0.000	0.005	0.003	0.015	0.065	0.030	0.002	0.047	-0.004	0.028	0.139	0.147	**1.000**	0.092	-0.002	-0.032
Depression	-0.063	0.021	0.008	-0.008	0.005	-0.003	0.020	0.032	0.018	0.029	0.084	0.012	0.004	0.010	0.028	0.049	0.030	0.012	0.043	0.005	0.027	0.096	0.079	0.092	**1.000**	0.003	-0.029
LDL	-0.108	0.042	-0.077	0.080	0.009	0.034	0.112	-0.028	-0.056	-0.039	-0.051	-0.028	-0.007	-0.014	0.000	-0.010	-0.003	-0.010	-0.013	-0.007	-0.044	0.010	0.016	-0.002	0.003	**1.000**	0.090
SBP	0.087	-0.002	-0.035	0.052	0.060	-0.029	0.040	-0.009	-0.042	-0.006	0.047	-0.014	-0.004	-0.006	-0.015	-0.014	-0.010	-0.007	-0.016	-0.005	-0.017	-0.017	-0.013	-0.032	-0.029	0.090	**1.000**

*Derived from Veterans Affairs database, June 2019