Prediction of Long Term Comparative Effectiveness of Once Weekly Semaglutide Versus Standard of Care in a Real World Adult US Population With Type 2 Diabetes - a Randomized Pragmatic Trial (SEPRA trial)

DUPLICATE – SEPRA

October 7, 2022

1. RCT Details

This section provides a high-level overview of an **ongoing** RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Long Term Comparative Effectiveness of Once Weekly Semaglutide Versus Standard of Care in a Real World Adult US Population With Type 2 Diabetes - a Randomized Pragmatic Trial (SEPRA trial) - NCT03596450

1.2 Intended aim(s)

To evaluate the effects of semaglutide injection (Ozempic®) on hemoglobin A1c (HbA1c) compared to the standard of care in patients with type 2 diabetes on metformin who are treated in a practice setting.

1.3 Primary endpoint for replication

Long-term glycemic control defined as proportion of patients who will achieve an HbA1c of less than 7.0% (53.0 mmol/mol) at 365 days after drug initiation.

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

The trial is estimated to enroll 1,387 patients.

1.5 Secondary endpoint for replication and RCT finding

Change in HbA1c from baseline at 365 days after drug initiation.
Number of hypoglycemic episodes leading to an inpatient admission or emergency room encounter.

1.6 Trial estimate

The trial is ongoing and scheduled to finalize the data collection for the primary outcome on June 9, 2023 (estimated primary completion date updated on 28 September 2022).

2. Person responsible for implementation of replication in Aetion

Elvira D'Andrea, MD, PhD, implemented the study design in the Aetion Evidence Platform and SAS 9.4. She is not responsible for the validity of the design and analytic choices. All implementation steps are recorded, and the implementation history is archived in the platform.

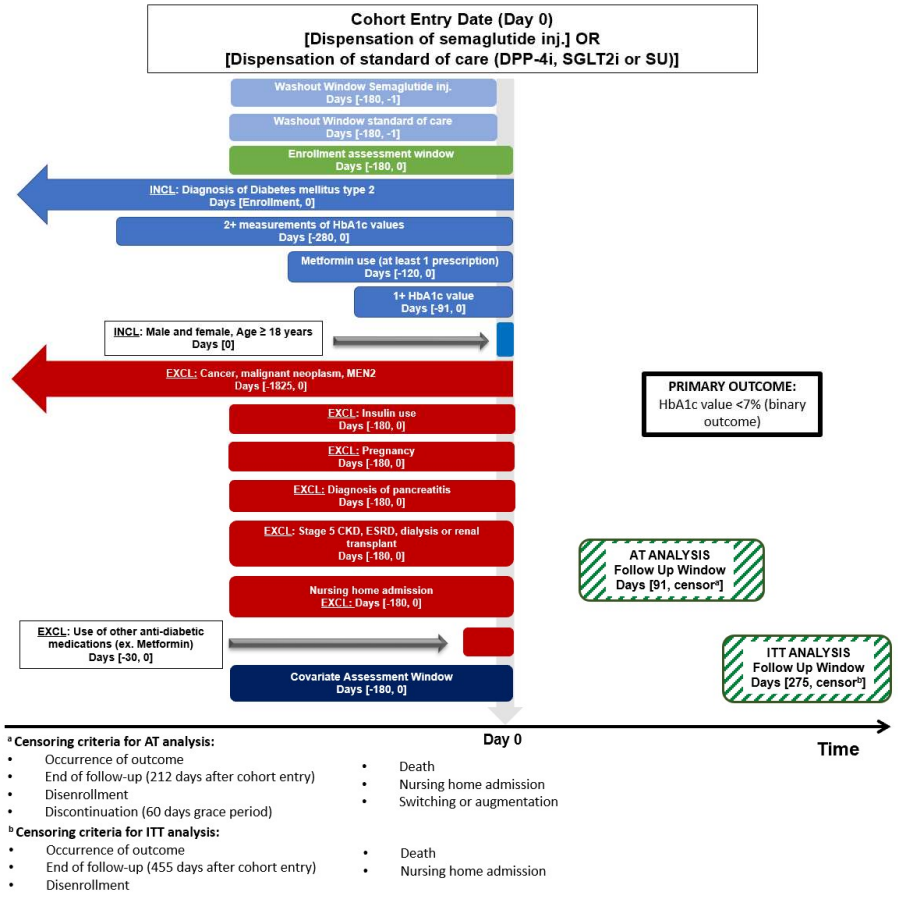
3. Data Source(s)

Optum® Clinformatics® Data Mart Database

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Figure 1. Design Diagram – SEPRA (SEMAGLUTIDE pRCT) TRIAL REPLICATION



5. Cohort Identification

Note. The feasibility counts were run on Optum® Clinformatics® version of Dec 23, 2021, for the study period between Dec 6, 2017, to Jun 30, 2021. The primary analysis will be run by implementing the protocol on refreshed data that includes data up to March 30, 2022. Therefore, the cohorts for the primary analyses are expected to be larger than those of the initial feasibility analyses presented in this protocol.

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort design comparing injectable subcutaneous semaglutide (once weekly) to standard of care, i.e., dipeptidyl peptidase 4 inhibitors (DPP-4i), sodium-glucose cotransporter 2 inhibitors (SGLT2i), other glucagon-like peptide-1 receptor agonists (GLP-1 RA) - except for semaglutide oral and injection -, or 2nd generation sulfonylureas (SU). Treatments in both arms are administered in combination with metformin. Patients will be required to have continuous enrollment during a baseline period of 180 days before initiation of semaglutide or standard of care. The analyses will be restricted to individuals with type 2 diabetes mellitus who are on treatment with metformin, defined as the presence of at least 1 prescription for metformin within 120 days (90 days + 30 days of grace period) before and including cohort entry. The information for emulating the trial implementation is collected from clinicaltrial.gov, version submitted on September 7, 2022 (NCT03596450), and questions to the trialists (responses received on September 26, 2022).

5.2 Important steps for cohort formation

New use of semaglutide injection (exposure) is defined as no use of the exposure drug within 180 days prior to index date. New use of standard of care (comparator) is defined as no use of the DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) or 2nd generation SU within 180 days prior to index date. Eligible patients are required to be new users with respect to both exposure and comparator groups, defined as no use of both exposure and comparator drugs within at least 180 days prior to index date.

5.2.1 Data Source

Optum® Clinformatics® Data Mart Database (CDM): Dec 6, 2017 – Jun 30, 2021

The study will be conducted in the de-identified Optum® CDM because this database is linked with national lab test provider chains. Thus, the results for outpatient laboratory tests (including test results of HbA1c) are available for a subset

of approximately 45% beneficiaries.

5.2.2 Eligible cohort entry dates

Semaglutide injection, for subcutaneous use, was first approved by FDA to improve glycemic control in adults with type 2 diabetes mellitus on Dec 5, 2017 (the approval of the comparator drugs for the same indication was antecedent to 2017). Thus, the initial eligible cohort entry date is the first date after the FDA approval available in the data.
Although the primary analysis of the trial used an "intention-to-treat" (ITT) approach - as implied on clinicaltrial.gov and confirmed by the trialists -, we conducted a secondary analysis using an "as-treated" (AT) approach because of the nature of the real-world data (please refer to paragraph 6.3.2 for further details). Based on this decision we created two study cohorts which differ by the last eligible date of cohort entry:

- **COHORT ITT** - The last eligible date for the cohort that will be analyzed with an "intent to treat" approach is Aug 31, 2020, ten months before the end of all available data in Optum® CDM. Since the effects of semaglutide, DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) and 2nd generation SU on the outcome will be estimated between 275 and 455 days after cohort entry, this will allow all eligible patients to contribute to the outcome (see Section 6.3).
- **COHORT AT** - The last eligible date for the cohort that will be analyzed with an "as-treated" approach is Feb 28, 2021, four months before the end of all available data in Optum® CDM. Since the effects of semaglutide, DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) and 2nd generation SU on the outcome will be estimated between 91 and 212 days after cohort entry, this will allow all eligible patients to contribute to the outcome (see Section 6.3).
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5.2.3 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

Note. Patients who do not start the follow up or are censored between cohort entry and the beginning of the outcome assessment window (i.e., **COHORT AT**: 0-90 days after cohort entry, **COHORT ITT**: 0-274 days after cohort entry) for the reasons reported in the Section 6.3.2 will not contribute to the baseline characteristics of the unmatched or matched cohorts. Further details on the number of patients who are excluded from the study cohort are reported in Section 7.

5.3 Flowchart of the study cohort assembly

Aetion link to the cohort creation of semaglutide vs. standard of care
COHORT AT: https://bwh-dope.aetion.com/cohorts/details/34150/1673/86399/basics

COHORT ITT: https://bwh-dope.aetion.com/cohorts/details/34149/1673/86398/basics

	Optum® COHORT AT		Optum® COHORT ITT	
	Excluded Patients	**Remaining Patients**	**Excluded Patients**	**Remaining Patients**
Patients in dataset		81,796,156		81,796,156
Patients meeting cohort entry criteria		1,391,063		1,267,388
Excluded due to insufficient enrollment	-185,893 (13%)	1,205,170	-157,177 (12%)	1,110,211
Excluded due to prior use of referent	-1,006,363 (84%)	198,807	-943,160 (85%)	167,051
Excluded due to prior use of exposure	-46,187 (23%)	152,620	-35,553 (21%)	131,498
Excluded because patient qualified in >1 exposure category	-164 (<1%)	152,456	-101 (<1%)	131,397
Excluded based on Inclusion Age ≥ 18	-34 (<1%)	152,422	-27 (<1%)	131,370
Excluded based on Exclusion for Age missing	-10 (<1%)	152,412	-6 (<1%)	131,364
Excluded based on Exclusion for Gender unknown/missing	-54 (<1%)	152,358	-44 (<1%)	131,320
Excluded based on Inclusion Type 2 diabetes mellitus	-8,127 (5%)	144,231	-6,929 (5%)	124,391
Excluded based on Inclusion Use of Metformin	-49,397 (34%)	94,834	-41,708 (34%)	82,683
Excluded based on Inclusion At least 2 HbA1c records within the prior 280 days	-48,281 (51%)	46,553	-42,342 (51%)	40,341
Excluded based on Inclusion At least 1 HbA1c record ≥ 7% within the prior 90 days	-5,365 (12%)	41,188	-4,644 (12%)	35,697
Excluded based on Exclusion Use of any other anti-diabetes medications	-893 (2%)	40,295	-857 (2%)	34,840
Excluded based on Exclusion Any insulin use	-2,114 (5%)	38,181	-1,881 (5%)	32,959
Excluded based on Exclusion Pregnancy	-3 (<1%)	38,178	-2 (<1%)	32,957
Excluded based on Exclusion Multiple Endocrine Neoplasia syndrome type 2	-0 (<1%)	38,178	-0 (<1%)	32,957
Excluded based on Exclusion CKD stage 5, ESRD, dialysis or renal transplant	-6 (<1%)	38,172	-5 (<1%)	32,952
Excluded based on Exclusion Nursing home admission	-129 (<1%)	38,043	-112 (<1%)	32,840
Patients in Exposure Group (Semaglutide injectable)		1,083		796
Patients in Referent Group (DPP-4i, SGLT2i, GLP-1 RA except semag., 2nd gen SU)		36,960		32,044
Final cohort		38,043		32,840

6. Variables

6.1 Exposure-related variables:

Study drug:

New initiation of injectable subcutaneous semaglutide (once weekly), a glucagon-like peptide-1 receptor agonist. New initiation is defined as no use of semaglutide within 180 days before treatment initiation (washout period). New users of semaglutide are not allowed to receive DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) or 2nd generation SU within 180 days prior to treatment initiation. Concurrent use of metformin is required.

Comparator agent:

New initiation of "standard of care" (oral). New initiation is defined as no use of DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) or 2nd generation SU within 180 days before treatment initiation (washout period). New users of DPP-4i, SGLT2i, GLP-1 RA (except semaglutide) or 2nd generation SU are not allowed to receive semaglutide within 180 days prior to treatment initiation. Concurrent use of metformin is required. In the pragmatic trial, "standard of care" was defined as commercially available antidiabetic medication other than semaglutide. In sensitivity analyses we will compare semaglutide with each of the drug classes included in the standard of care separately.

6.2 Preliminary Covariates:

- Age
- Gender
- Combined Comorbidity Index (CCI), measured over the baseline covariate assessment period, defined as 180 days prior to and including index date.

Covariates listed above represent only a small subset of covariates that will ultimately be controlled for in the design and analysis. We use the covariates above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (**Appendix B**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix A**):

- **Primary outcome:**
  - Proportion of patients who achieve an HbA1c of less than 7.0% (53.0 mmol/mol) at the HbA1c test closest to 365 days (allowable range: 275 to 455 days) after treatment initiation (ITT analysis, see paragraph 6.3.2.2).
- **Secondary outcome**:
  - Proportion of participants who will achieve an HbA1c of less than 7.0% (53.0 mmol/mol) at the HbA1c test closest to 26 weeks (allowable range: 12 weeks to 30 weeks) after treatment initiation (AT analysis, see paragraph 6.3.2.1)
  - Changes in HbA1c from baseline to 26 weeks (AT analysis, see paragraph 6.3.2.1) or to 52 weeks (ITT analysis, see paragraph 6.3.2.2) after treatment initiation.
  - Number of hypoglycemic episodes leading to an inpatient admission or emergency room encounter (AT analysis, see paragraph 6.3.2.1)

Note. In the emulation, as well as in the pragmatic trial, the *HbA1c at baseline* is defined as the last recorded HbA1c value measured within 91 days before and including cohort entry date. The *HbA1c at the end of follow-up* is defined as the recorded HbA1c value closest to 365 days and measured between 275 and 455 days (1 year +/- 90 days) after cohort entry for the ITT analysis and the recorded HbA1c value closest to 182 days (26 weeks) and measured between 91 and 212 days (12-30 weeks) after cohort entry for the AT analysis.

6.3.2 Primary analysis and study follow-up

Based on the information reported on clinicaltrial.gov and the answers received after contacting the SEPRA trialists, we learnt that dedicated study visits are programmed at randomization, at year 1, and at year 2 post-randomization. The study will also capture data collected at the sites during routine diabetic care visits, i.e., office visits and other patient contacts that occur as part of routine clinical practice. Routine diabetic care visits will occur per study physician's routine clinical practice, therefore the number of visits and data available may differ from site to site and patient to patient. The outcome (HbA1c value) at baseline is defined as an HbA1c value recorded ≤ 90 days prior to randomization visit (week 0). The dedicated visit at 1 year is performed by the trialists at 52 (± 10) weeks) after randomization. If endpoint data at year 1 is missing or outside of 52 ± 10 weeks, then the routine diabetic care data closest to 52 weeks post-randomization ±10 weeks will be used. If no routine diabetic care data are available 52 (± 10) weeks post-randomization, then year 1 endpoint data will be considered missing and imputed, if applicable.

Because of anticipated shorter follow-up time in our data, we will not replicate the results of the trial at 2 years post-randomization.

Our RWE study will use an ITT analysis that disregards changes in treatment over the course of 1 year follow up as the primary analysis. However, to address potential differences in adherence due to measures or initiatives applied by the researchers of the SEPRA trial (e.g., routine calls, incentives etc.) and the high discontinuation rates in clinical practice, our emulation will include a secondary analysis focused on "as-treated" (AT) analysis which censors patients when they discontinue or switch treatments. In both ITT and AT analyses, the treatment drug will be defined as the index drug assigned on the day of cohort entry. Both analyses will use 1:1 nearest-neighbor matching on the propensity score to adjust for confounding with a matching caliper of 0.01.

6.3.2.1 ITT analysis

In the ITT analysis patients will be followed between 275 and 455 days after cohort entry (1 year +/- 3 months). The outcome assessment window will start 275 days after cohort entry date and will continue until the earliest date of the following events:

- Occurrence of the outcome of interest (HbA1c value measured closest to 365 days after cohort entry),
- End of continuous registration in the database (disenrollment or end of available data),
- End of the study period,
- Death,
- Nursing home admission.

6.3.2.2 AT analysis

In the AT analysis patients will be followed between 91 and 212 days after cohort entry. The outcome assessment window will start 91 days after cohort entry date and will continue until the earliest date of the following events:

- Occurrence of the outcome of interest (HbA1c value closest to 182 days, measured between 91 and 212 days after cohort entry),
- End of continuous registration in the database (disenrollment or end of available data),
- End of the study period,
- Death,

- Index drug discontinuation (discontinuation is defined by a gap of more than 60 days following the last days supply, episodes of treatment less than 60 days apart are bridged and treated as continuously exposed during the gap),
- Crossover or addition of drug from the other treatment group,
- Switching between the drug classes of the comparator group (i.e., DPP-4i to SGLT2i or SU or GLP-1 RA except semaglutide, SGLT2i to DPP-4i or SU or GLP-1 RA except semaglutide, SU to DPP-4i or SGLT2i or GLP-1 RA except semaglutide)
- Addition of any other anti-diabetic medications,
- Nursing home admission (nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on drug utilization after admission. For the same reason we will exclude nursing home residents from our cohorts).

6.3.2.3 ITT analysis

In the ITT analysis patients will be followed between 275 and 455 days after cohort entry (1 year +/- 3 months). The outcome assessment window will start 275 days after cohort entry date and will continue until the earliest date of the following events:

- Occurrence of the outcome of interest (HbA1c value measured closest to 365 days after cohort entry),
- End of continuous registration in the database (disenrollment or end of available data),
- End of the study period,
- Death,
- Nursing home admission.

6.3.3 Sensitivity analyses:

- Evaluate primary and secondary outcomes using fine stratification on the propensity score instead of 1:1 matching to boost power
- Evaluate primary and secondary outcomes using each of the 3 drug classes included in the standard of care definition as the comparator (DPP-4i, SGLT2i, GLP-1 RA except semaglutide, or 2nd generation SU) to better understand class effects

Note. To decrease the incidence of missing values of the outcome, we required that the eligible patients had at least 2 HbA1c measurements recorded within 280 days before and including cohort entry. This increases the probability of including in the final cohort patients who are adherent to a routinely HbA1c testing and, consequently, will decrease the frequency of missing values of the

outcome. After assessing the diagnostics for different techniques to handle missing values (i.e., complete case analysis, multiple imputation, and IPCW) of the outcome, we decided to apply the multiple imputation technique to the primary analysis and test the robustness of the results with a sensitivity analysis applying the complete case analysis technique.

7. Initial Feasibility Analysis

Aetion report name:

For semaglutide vs. standard of care

Optum® CDM [AT analysis: proper outcome assessed within 91-212 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86429

Optum® CDM [ITT analysis: proper outcome assessed within 275-455 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86428

Optum® CDM [AT analysis: dummy outcome assessed within 91-212 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86431

Optum® CDM [ITT analysis: dummy outcome assessed within 275-455 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86430

Date conducted: 09/29/2022

Complete Aetion feasibility analysis using age and CCI as the only covariates and the primary outcome (Section 6.3). No measures of association will be computed nor will mean and standard deviation of the HbA1c outcome stratified by treatment group.

- Report patient characteristics by treatment group

  For semaglutide vs. standard of care

	BEFORE 1:1 PS MATCHING on AGE, CCI					
	Optum CDM – COHORT AT			Optum CDM – COHORT ITT		
	Standard of care-Comparator	**Semaglutide inj. - Exposure**	**Difference**	**Standard of care-Comparator**	**Semaglutide inj. - Exposure**	**Difference**
Number of patients *	18,706	682	- (-, -)	26,541	635	- (-, -)
Age						
...mean (sd)	65.27 (11.34)	56.87 (11.91)	8.40 (7.49, 9.31)	64.75 (11.55)	56.80 (11.95)	7.94 (7.00, 8.89)
...median [IQR]	67.00 [59.00, 73.00]	57.00 [48.00, 66.00]	- (-, -)	67.00 [58.00, 73.00]	57.00 [48.00, 67.00]	- (-, -)
Gender						
...M = MALE; n (%)	10,545 (56.4%)	331 (48.5%)	7.8% (3.9%, 11.7%)	14,310 (53.9%)	302 (47.6%)	6.4% (2.3%, 10.4%)
...F = FEMALE; n (%)	8,161 (43.6%)	351 (51.5%)	-7.8% (-11.7%, -3.9%)	12,231 (46.1%)	333 (52.4%)	-6.4% (-10.4%, -2.3%)
Combined Comorbidity Score - CCI (180 days)						
...mean (sd)	1.31 (1.97)	1.11 (1.68)	0.20 (0.07, 0.33)	1.37 (1.98)	1.06 (1.60)	0.31 (0.19, 0.44)
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	- (-, -)	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	- (-, -)

* Patients who were censored between cohort entry and the beginning of the outcome assessment window are excluded and will not contribute to the unmatched or matched cohorts.

	AFTER 1:1 PS MATCHING on AGE, CCI					
	Optum CDM – COHORT AT			Optum CDM – COHORT ITT		
	Standard of care-Comparator**	**Semaglutide inj. - Exposure**	**Difference**	**Standard of care-Comparator****	**Semaglutide inj. - Exposure**	**Difference**
Number of patients *	682	682	- (-, -)	635	635	- (-, -)
Age						
...mean (sd)	56.87 (11.91)	56.87 (11.91)	0.00 (-1.26, 1.26)	56.80 (11.95)	56.80 (11.95)	0.00 (-1.32, 1.32)
...median [IQR]	57.00 [48.00, 66.00]	57.00 [48.00, 66.00]	- (-, -)	57.00 [48.00, 67.00]	57.00 [48.00, 67.00]	- (-, -)
Gender						
...M = MALE; n (%)	402 (58.9%)	331 (48.5%)	10.4% (5.0%, 15.8%)	366 (57.6%)	302 (47.6%)	10.1% (4.5%, 15.7%)
...F = FEMALE; n (%)	280 (41.1%)	351 (51.5%)	-10.4% (-15.8%, -5.0%)	269 (42.4%)	333 (52.4%)	-10.1% (-15.7%, -4.5%)
Combined Comorbidity Score - CCI (180 days)						
...mean (sd)	0.97 (1.72)	1.11 (1.68)	-0.14 (-0.32, 0.04)	1.02 (1.81)	1.06 (1.60)	-0.05 (-0.23, 0.14)
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	- (-, -)	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	- (-, -)

* Patients who were censored between cohort entry and the beginning of the outcome assessment window are excluded and will not contribute to the unmatched or matched cohorts.

- Report summary parameters of study population **FEASIBILITY- FOR STUDY OUTCOME**
  For semaglutide vs. standard of care

	Optum CDM COHORT AT	Optum CDM COHORT ITT
Number of patients in full cohort	38,043	32,840
Number of patients who did not begin follow-up *	18,655	5,664
Number of patients in the analytic cohort	19,388	27,176
Number of events**	4,203	6,481
Number of patients with an HbA1c value recorded during follow-up	9,671	16,965
Number of patients in group (before matching): Standard of care	18,706	26,541
Number of patients in group (before matching): Semaglutide	682	635
Number of patients in group (after matching): Standard of care	682	635
Number of patients in group (after matching): Semaglutide	682	635
Risk per 1,000 patients	216.78	238.48

* Patients who were censored between cohort entry and the beginning of the outcome assessment window.
** Patients with HbA1c < 7% recorded between 91-212 days after cohort entry in the cohort AT and between 275-455 days after cohort entry in the cohort ITT.

- Report median follow-up time by treatment group

  For semaglutide vs. standard of care

	Median Follow-Up Time (Days) [IQR] – AT analysis*	Median Follow-Up Time (Days) [IQR] – ITT analysis*
Patient Group	**Optum CDM – COHORT AT**	**Optum CDM - COHORT ITT**
Overall Patient Population	70 [37, 121]	165 [66, 180]
Referent	86 [51, 121]	180 [82, 180]
Exposure	58 [28, 116]	122 [54, 180]

* The median follow-up time is defined as the median number of days that a patient is followed within the outcome assessment window, which begins 91 days and ends 212 days after the cohort entry date for the COHORT AT, and it begins 275 days and ends 455 days after the cohort entry date for the COHORT ITT

- Report reasons for censoring in the overall study population after matching

For semaglutide vs. standard of care – COHORT AT

	Overall N = 1,364	Standard care (DPP-4i, SGLT-2ra, SU) N = 682	Semaglutide N = 682
Dummy outcome*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	1 (0.1%)	1 (0.1%)	0 (0.0%)
Maximum follow-up time	667 (48.9%)	349 (51.2%)	318 (46.6%)
End of patient data	58 (4.3%)	22 (3.2%)	36 (5.3%)
End of patient enrollment	96 (7.0%)	48 (7.0%)	48 (7.0%)
Augmentation or Switching to other antidiabetic drugs; switching between comparator classes; nursing home admission; discontinuation of metformin, semaglutide or standard of care (with 60 days of grace period)	542 (39.7%)	262 (38.4%)	280 (41.1%)

* dummy outcome of a 90-day gap in database enrollment

For semaglutide vs. standard of care – COHORT ITT

	Overall N = 1,270	Standard care (DPP-4i, SGLT-2ra, SU) N = 635	Semaglutide N = 635
Dummy outcome*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	6 (0.5%)	4 (0.6%)	2 (0.3%)
Maximum follow-up time	861 (67.8%)	472 (74.3%)	389 (61.3%)
End of patient data	267 (21.0%)	80 (12.6%)	187 (29.4%)
End of patient enrollment	123 (9.7%)	73 (11.5%)	50 (7.9%)
Nursing home admission	13 (1.0%)	6 (0.9%)	7 (1.1%)

* dummy outcome of a 90-day gap in database enrollment

- Report the overall risk of the primary outcome

  For semaglutide vs. standard of care

	COHORT AT Semaglutide vs Standard of care	COHORT ITT Semaglutide vs Standard of care
Outcome	216.78	238.48

8. Initial Power Assessment

Analysis report name:

For semaglutide vs. standard of care

Optum® CDM [AT analysis – outcome window within 91-212 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86429

Optum® CDM [ITT analysis – outcome window within 275-455 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86428

Without the SEPRA protocol, we were unable to ascertain the assumptions of the trial's power calculation. However, we assume that our power is similar to the power in the trial because we anticipate that the refreshed Optum Clinformatics data on which we will run our primary analysis will result in cohorts that exceed the target number of participants in each arm of the trial (see Table below)."

	N. patients in the trial	**N. of patients in the matched COHORT AT***	**N. of patients in the matched COHORT ITT***
All patients	1,378	1,364	1,270
Reference	689	682	635
Exposed	689	682	635

* The feasibility counts were run on Optum® Clinformatics® version released on Dec 23, 2021, for the study period of Dec 6, 2017, to Jun 30, 2021. The primary analysis will be run by implementing the protocol on refreshed data that includes data up to March 30, 2022. Therefore, the cohorts for the primary analyses are expected to be larger than those of the initial feasibility analyses presented in this protocol.

Date conducted: 09/29/2022

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, gender and combined comorbidity index.

- Stop analyses until feasibility and power are reviewed by primary investigators and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

Reviewed by PI:	Shirley Wang	Date reviewed:	
Reviewed by FDA:	Ken Quinto	Date reviewed:	
Reasons for stopping analysis (if required):			

9. Balance Assessment

For semaglutide vs. standard of care

Optum® CDM [AT analysis – outcome window within 91-212 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86487

Optum® CDM [ITT analysis – outcome window within 275-455 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86486

Date conducted:

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates. In the feasibility analysis, calendar time is included in the PS model as continuous variable, using quarters as unit of measurement, while in the primary analysis the unit measurement for calendar time will be days.

- Provide plot of PS distributions stratified by treatment group.

  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report follow-up time by treatment group after matching.

  For semaglutide vs. standard of care

	Median Follow-Up Time (Days) [IQR] – AT analysis*	**Median Follow-Up Time (Days) [IQR] – ITT analysis***
Patient Group	**Optum CDM – COHORT AT**	**Optum CDM - COHORT ITT**
Overall Patient Population	80 [42, 121]	129 [60, 180]
Referent	81 [43, 121]	136 [66, 180]
Exposure	58 [28, 116]	122 [54, 180]

* The median follow-up time is defined as the median number of days that a patient is followed within the outcome assessment window, which begins 91 days and ends 212 days after the cohort entry date for the COHORT AT, and it begins 275 days and ends 455 days after the cohort entry date for the COHORT ITT

- Report reasons for censoring by treatment group after matching.

  For semaglutide vs. standard of care – COHORT AT

	Overall N = 1,352	Standard care (DPP-4i, SGLT-2ra, SU) N = 678	Semaglutide N = 678
Dummy outcome*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	1 (0.1%)	1 (0.1%)	0 (0.0%)
Maximum follow-up time	667 (49.2%)	351 (51.8%)	316 (46.6%)
End of patient data	75 (5.5%)	39 (5.8%)	36 (5.3%)
End of patient enrollment	95 (7.0%)	48 (7.1%)	47 (6.9%)
Augmentation or Switching to other antidiabetic drugs; switching between comparator classes; nursing home admission; discontinuation of metformin, semaglutide or standard of care (with 60 days of grace period)	518 (38.2%)	239 (35.3%)	279 (41.2%)

* dummy outcome of a 90-day gap in database enrollment

For semaglutide vs. standard of care – COHORT ITT

	Overall N = 1266	Standard care (DPP-4i, SGLT-2ra, SU) N = 633	Semaglutide N = 633
Dummy outcome*	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	5 (0.4%)	3 (0.5%)	2 (0.3%)
Maximum follow-up time	743 (58.7%)	355 (56.1%)	388 (61.3%)
End of patient data	406 (32.1%)	219 (34.6%)	187 (29.5%)
End of patient enrollment	102 (8.1%)	53 (8.4%)	49 (7.7%)
Nursing home admission	10 (0.8%)	3 (0.5%)	7 (1.1%)

* dummy outcome of a 90-day gap in database enrollment

- Report the overall risk of the primary outcome

	COHORT AT Semaglutide vs Standard of care	COHORT ITT Semaglutide vs Standard of care
Outcome	214.57	232.60

10. Final Power Assessment

Date conducted: 9/30/2022

Analysis report name:

For semaglutide vs. standard of care

Optum® CDM [AT analysis – outcome window within 91-212 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86433

Optum® CDM [ITT analysis – outcome window within 275-455 days after cohort entry]: https://bwh-dope.aetion.com/projects/details/1673/rwrs/86432

Without the SEPRA protocol, we were unable to ascertain the assumptions of the trial's power calculation. However, we assume that our power is similar to the power in the trial because we anticipate that the refreshed Optum Clinformatics data on which we will run our primary analysis will result in cohorts that exceed the target number of participants in each arm of the trial (see Table below)."

	N. patients in the trial	**N. of patients in the matched COHORT AT***	**N. of patients in the matched COHORT ITT***
All patients	1,378	1,352	1,266
Reference	689	678	633
Exposed	689	678	633

* The feasibility counts were run on Optum® Clinformatics® version released on Dec 23, 2021, for the study period of Dec 6, 2017, to Jun 30, 2021. The primary analysis will be run by implementing the protocol on refreshed data that includes data up to March 30, 2022. Therefore, the cohorts for the primary analyses are expected to be larger than those of the initial feasibility analyses presented in this protocol.

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:		Date reviewed:	
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:
Date votes and concerns are summarized:

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.
- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the success of the RWD study in the Google Form. This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.
- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

12. Register study protocol on clinicalTrials.gov

Date conducted:

- Register the study on clinicalTrials.gov and upload this document.

13. Comparative Analyses

Aetion report name:
Date conducted:

13.1 For primary analysis:

13.2 For sensitivity analyses:

14. Requested Results

14.1 Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	Exposure	Std. diff.	Referent	Exposure	Std. diff.
Number of patients			-			-
Age categories						
…						

14.2 Table 2: Follow-up time

Patient Group	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	
Referent	
Exposure	

14.3 Table 3: Censoring events

	Overall	Referent	Exposure
Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
…			

14.4 Table 4: Results from primary analyses.

Analysis	No. exposed events	No. referent events	Exposed rate	Referent rate	HR (95% CI)
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

14.5 Table 5: Results from secondary analyses.

15. References

ClinicalTrials.gov Identifier: NCT03596450. Long Term Comparative Effectiveness of Once Weekly Semaglutide Versus Standard of Care in a Real World Adult US Population With Type 2 Diabetes - a Randomized Pragmatic Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT03596450 Accessed 9/28/2022.

Appendix A: Flowchart

#	SEPRA Trial		References/Rationale	Color coding
			Please see the following Google Drive for further details or any missing information: https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV?usp=sharing	Criteria
	Trial details - clinicaltrial.gov NCT03596450		**ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/ backward mapping based on the CMS ICD-9 to ICD-10 mapping:** https://www.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html	Adequate mapping in claims
	EXPOSURE FROM Trial			Intermediate mapping in claims
	Arm	**Intervention/Treatment**		Poor mapping or cannot be measured in claims
	Exposure: **Semaglutide injection** (Ozempic®) in addition to **metformin monotherapy** as treatment intensification in the course of routine clinical practice. Reference: **Standard of care** (oral or injectable) in addition to **metformin monotherapy** as treatment intensification in the course of routine clinical practice. Standard of care is defined as commercially available oral or injectable antidiabetic medication other than semaglutide. Aim: To evaluate the effects of semaglutide injection (Ozempic®) compared to other treatments on HbA1c reduction in patients with type 2 diabetes in a practice setting.	Exposure: new use of Semaglutide injection (washout **180 days**) in combination with metformin **NDC Generic Name:** SEMAGLUTIDE [route of administration: injection, subcutaneous] **NDC Brand name:** OZEMPIC Reference: new use of GLP-1ra (except for semaglutide oral or inj.), DPP-4i, SGLT-2i, 2nd generation sulfonylureas (washout **180 days**) **NDC Name:** please refer to "Reference name list"		Cannot be measured in claims but not important for the analysis
	PRIMARY OUTCOME			Not reported in the list of eligibility criteria but included in the emulation for specific reasons
	Hemoglobin A1c (HbA1c) less than 7.0% (53 mmol/mol) (yes/no) [Time frame 1 year]	**Measured as recorded HbA1c value [binary: <7% or ≥7%] between 275 and 455 days and closest to 365 days after drug initiation (ITT ANALYSIS) or closest to 182 days between 91 and 212 days after cohort initiation (AT ANALYSIS):** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0	**The Loinc codes have been selected based on an evaluation of all available Loinc codes for HbA1c in the claims**	
	INCLUSION CRITERIA			
#	Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study.	N/A		
1	Male or female, age 18 years or older at the time of signing informed consent.	Female and male, ≥ 18 years at the time of drug initiation		
2	Type 2 diabetes mellitus diagnosis	**Measured from the time of enrollment to the day of drug initiation in inpatient (any position) or outpatient (any position) settings:** Type 2 diabetes: ICD 9 diagnosis: 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 ICD 10 diagnosis: E11.x		
3	Treatment with either 1 or 2 oral antidiabetic medications.	**3.1 At least one prescription of metformin within 90 days (+30 days) before cohort entry in both treatment groups** Generic name: Metformin Hcl (see also exclusion criterion #1)		
4	Recorded HbAlc value within last 90 days prior to randomization.	**4.1 Selection of all patients with 2 measurements of HbA1c values (between 2-20%) recorded within 280 days prior to and including cohort entry:** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0 **4.2 Selection of patients with at least one measurement of HbA1c ≥7% value recorded within the last 91 days prior to and including cohort entry:** Loinc codes: 17855-8, 17856-6, 41995-2, 43150-2, 4548-4, 4549-2, 55454-3, 71875-9, 74246-0		
#	Further intensification with an additional antidiabetic oral or injectable medication is indicated to achieve glycemic target at the discretion of the study physician according to approved labelling	N/A		
#	Current member of a commercial or Medicare health plan with pharmacy benefits.	Optum (The database has been selected due to the information on the laboratory results/values of HbA1c)		
	EXCLUSION CRITERIA			

Appendix A: Flowchart

#			
#	Previous randomization in this study	N/A	
#	Participation in another clinical trial	N/A	
1	Treatment with any medication for the indication of diabetes other than metformin in a period of 30 days before the day of eligibility assessment.	**Measured 180 days prior to and including the day of drug initiation inpatient (any position), outpatient (any position):** The list of drugs (generic names) is reported under "Other anti-diabetic treatments (other than insulin)" in the tab "Other anti-diabetic treatments"	NB. Washout period extended to 180 days consistently with the washout period of the ther 2nd line thrapy agents (comparator group: standard of care) and insulin
2	Treatment with insulin (Temporary/emergency use of any type of insulin is allowed, as is prior insulin treatment for gestational diabetes)	**Measured 180 days prior to and including day of drug initiation:** <u>NDC Generic Name:</u> The definition of insulin (generic names) is reported under "Insulin" in the tab "Other anti-diabetic treatments"	NB. Washout period extended to 180 days to exclude prevalent users (i.e. patients on active insulin therapy) from the cohort.
3	Female who is pregnant, breastfeeding or intends to become pregnant	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Please refer to "Pregnancy definition"	
4	Contraindications to semaglutide according to the Food and Drug Administration approved label	**Measured 1825 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** **Contraindications to Semaglutide as reported on the FDA approved label:** <u>Personal or family history of medullary thyroid carcinoma:</u> n/a <u>Multiple Endocrine Neoplasia syndrome type 2:</u> ICD-9 diagnosis: 258.02, 258.03 ICD-10 diagnosis: E31.22, E31.23	
5	CKD stage 5, End-stage renal disease, dialysis or renal transplant	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** <u>CKD stage 5, End-stage renal disease, dialysis or renal transplant:</u> ICD-9 diagnosis: 585.5, 585.6, 996.81, V42.0, V45.1x, V56.xx ICD-9 procedure: 39.95, 54.98, 55.6x ICD-10 diagnosis: N18.5, N18.6, R88.0, T82.41, T82.42, T82.49, T85.611, T85.621, T85.631, T86.1x, Y84.1, Z48.22, Z49.xx, Z91.15, Z94.0, Z99.2 ICD-10 procedure: 0TY00Zx, 0TY10Zx, 3E1M39Z, 5A1Dx0Z CPT: 50360, 50365, 90920, 90921, 90924, 90925, 90935, 90937, 90939, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90989, 90993, 90999, 90997, 99512, 99559, 99512, G0257, G0314, G0315, G0316, G0317, G0318, G0319, <u>G0322, G0323, G0326, G0327, S9335, S9339</u>	N.B. criterion added to address potential residual confounding for the comparisons Semaglutide vs SGLT2i as a control reference N.B.2 Metformin - required by the study design in both exposure and comparator group - is contraindicated in patients with chronic kidney disease (CKD) with a glomerular filtration rate (GFR) < 30 mL/min.
6	Nursing home admission	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** <u>Place of Service Code:</u> 31 = SKILLED NURSING FACILITY 32 = NURSING FACILITY 33 = CUSTODIAL CARE FACILITY 34 = HOSPICE <u>Discharge Status Code is any of:</u> 03 = DISCHARGED/TRANSFERRED TO SKILLED NURSING FACILITY (SNF)WITH MEDICARE 64 = DISCHARGED/TRANSFERRED TO A NURSING FACILITY CERT UND MEDICARE 83 = RESERVED FOR NATIONAL ASSIGNMENT 93 = RESERVED FOR NATIONAL ASSIGNMENT	N.B. criterion added to address in real-world data potential outcome misclassification bias due to the lack of available information in most patients admitted in nursing home facilities

Appendix A: Attrition Table

OPTUM

Semaglutide vs standard of care

	Optum® COHORT AT	Optum® COHORT ITT
	Less Excluded Patients	**Less Excluded Patients**
Patients in dataset		
Patients meeting cohort entry criteria		
Excluded due to insufficient enrollment	-185,893 (13%)	-157,177 (12%)
Excluded due to prior use of referent	-1,006,363 (84%)	-943,160 (85%)
Excluded due to prior use of exposure	-46,187 (23%)	-35,553 (21%)
Excluded because patient qualified in >1 exposure category	-164 (<1%)	-101 (<1%)
Excluded based on Inclusion Age ≥ 18	-34 (<1%)	-27 (<1%)
Excluded based on Exclusion for Age missing	-10 (<1%)	-6 (<1%)
Excluded based on Exclusion for Gender unknown/missing	-54 (<1%)	-44 (<1%)
Excluded based on Inclusion Type 2 diabetes mellitus	-8,127 (5%)	-6,929 (5%)
Excluded based on Inclusion Use of Metformin	-49,397 (34%)	-41,708 (34%)
Excluded based on Inclusion At least 2 HbA1c records within the prior 280 days	-48,281 (51%)	-42,342 (51%)
Excluded based on Inclusion At least 1 HbA1c record ≥ 7% within the prior 90 days	-5,365 (12%)	-4,644 (12%)
Excluded based on Exclusion Use of any other anti-diabetes medications	-893 (2%)	-857 (2%)
Excluded based on Exclusion Any insulin use	-2,114 (5%)	-1,881 (5%)
Excluded based on Exclusion Pregnancy	-3 (<1%)	-2 (<1%)
Excluded based on Exclusion Multiple Endocrine Neoplasia syndrome type 2	-0 (<1%)	-0 (<1%)
Excluded based on Exclusion CKD stage 5, ESRD, dialysis or renal transplant	-6 (<1%)	-5 (<1%)
Excluded based on Exclusion Nursing home admission	-129 (<1%)	-112 (<1%)
Final cohort		

Appendix A: Trial Information

Information from Trial

Trial Name: SEPRA
https://clinicaltrials.gov/ct2/show/NCT03596450

NCT: NCT03596450

Therapeutic Area: Diabetes

RCT Category:

Sponsors and Collaborators:
Novo Nordisk A/S

Year: July 13, 2018 – June 9, 2023

Measurable Endpoint: The primary outcome is Hemoglobin A1c (HbA1c) less than 7.0% (53 mmol/mol).

Active Comparators:
Semaglutide
Standard of care

Population: Patients with type 2 diabetes who have previously been treated with metformin.

No. of Patients: 1,387

Power: Without the SEPRA protocol, we were unable to ascertain the assumptions of the trial's power calculation.

Appendix A: Codes

Reference - NDC Generic name:
DPP-4 Inhibitors
ALOGLIPTIN BENZOATE
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE
SAXAGLIPTIN HCL/METFORMIN HCL
LINAGLIPTIN
ALOGLIPTIN BENZOATE/METFORMIN HCL
ALOGLIPTIN BENZOATE/PIOGLITAZONE HCL
EMPAGLIFLOZIN/LINAGLIPTIN
SAXAGLIPTIN HCL
SITAGLIPTIN PHOSPHATE/METFORMIN HCL
SITAGLIPTIN PHOSPHATE/SIMVASTATIN
SITAGLIPTIN PHOSPHATE
SGLT-2 Inhibitors
CANAGLIFLOZIN
CANAGLIFLOZIN/METFORMIN HCL
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
ERTUGLIFLOZIN PIDOLATE
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE
DAPAGLIFLOZIN PROPANEDIOL/METFORMIN HCL
EMPAGLIFLOZIN/LINAGLIPTIN
EMPAGLIFLOZIN
DAPAGLIFLOZIN PROPANEDIOL
ERTUGLIFLOZIN PIDOLATE/METFORMIN HCL
EMPAGLIFLOZIN/METFORMIN HCL
2nd Generation Sus
GLIPIZIDE/METFORMIN HCL
GLYBURIDE,MICRONIZED
GLYBURIDE/METFORMIN HCL
GLYBURIDE
GLIPIZIDE
GLIMEPIRIDE
PIOGLITAZONE HCL/GLIMEPIRIDE
ROSIGLITAZONE MALEATE/GLIMEPIRIDE
GLP-1 RA (excluding semaglutide injection/subcutaneous)
ALBIGLUTIDE
DULAGLUTIDE
EXENATIDE
EXENATIDE MICROSPHERES
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG/LIXISENATIDE
LIXISENATIDE
LIRAGLUTIDE
INSULIN DEGLUDEC/LIRAGLUTIDE
SEMAGLUTIDE (route of adminitration: oral)

Appendix A: Codes

PREGNANCY DEFINITION	
1. Delivery Codes	
Procedure Codes	**Description**
CPT-4 codes	
1960	Anesthesia for vaginal delivery only
1961	Anesthesia for cesarean delivery only
1962	Anesthesia for urgent hysterectomy following delivery
1963	Anesthesia for cesarean hysterectomy w/o any labor analgesia/anesthesia care
1967	Neuraxial labor analgesia/anesthesia, planned vaginal delivery
1968	Anesthesia for cesarean delivery following neuraxial labor analgesia/anesthesia
1969	Anes for cesarean hysterectomy following neuraxial labor analgesia/anesthesia
59050	Fetal monitoring in labor, physician w/written report; s & i
59051	Fetal monitoring in labor, physician w/written report; intrepretation only
59400	ROUTINE TOTAL OBSTETRIC CARE including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care.
59409	Vaginal delivery only (w/wo episiotomy &/or forceps)
59410	Vaginal delivery only (w/wo episiotomy &/or forceps); w/postpartum care
59412	Ext cephalic version, w/wo tocolysis
59414	Delivery of placenta (separate proc)
59430	Postpartum care only
59510	Routine obstetric care w/antepartum care, cesarean delivery, & postpartum care
59514	Cesarean delivery only
59515	Cesarean delivery only; w/postpartum care
59525	Subtotal/total hysterectomy after cesarean delivery
59610	Routine obstetric care including antepartum care, vaginal delivery (with or without episiotomy, and/or forceps) and postpartum care, after previous cesarean delivery
59612	Vaginal delivery only, after previous cesarean delivery (with or without episiotomy and/or forceps)
59614	Vaginal delivery only, previous cesarean delivery w/postpartum care
59618	Routine obstetric care including antepartum care, cesarean delivery, and postpartum care, following attempted vaginal delivery after previous cesarean delivery
59620	Cesarean delivery after failed vaginal delivery, previous cesarean delivery
59622	Cesarean delivery after failed vaginal delivery, previous cesarean delivery; w/postpartum care
99436	Attendance at delivery, at request of delivering physician, & stabilization of newborn
99440	Newborn resuscitation
ICD-9 procedure codes	
72.xx	Forceps, vacuum, & breech
73.xx	Other including manual delivery
74xx	Cesarean section
75.4x	Manual removal of placenta
ICD-10 procedure codes	
Normal Delivery	
10E0XZZ	Delivery of Products of Conception, External Approach
C-Section	
10D00Z0	Extraction of Products of Conception, High, Open Approach
10D00Z1	Extraction of Products of Conception, Low, Open Approach
10D00Z2	Extraction of Products of Conception, Extraperitoneal, Open Approach
Other assisted delivery (forceps, vacuum, internal version, other)	
10D07Z3	Extraction of Products of Conception, Low Forceps, Via Natural or Artificial Opening
10D07Z4	Extraction of Products of Conception, Mid Forceps, Via Natural or Artificial Opening
10D07Z5	Extraction of Products of Conception, High Forceps, Via Natural or Artificial Opening
10D07Z6	Extraction of Products of Conception, Vacuum, Via Natural or Artificial Opening
10D07Z7	Extraction of Products of Conception, Internal Version, Via Natural or Artificial Opening
10D07Z8	Extraction of Products of Conception, Other, Via Natural or Artificial Opening
2. Identify preterm births	
a. Codes that have a specific gestational age mentioned	
ICD-9 code	Definition
765.21	Less than 24 completed weeks of gestation
765.22	24 completed weeks of gestation
765.23	25-26 completed weeks of gestation
765.24	27-28 completed weeks of gestation
765.25	29-30 completed weeks of gestation
765.26	31-32 completed weeks of gestation
765.27	33-34 completed weeks of gestation
765.28	35-36 completed weeks of gestation
ICD-10 code	Definition
P07.21	Extreme immaturity of newborn, gestational age less than 23 completed weeks
P07.22	Extreme immaturity of newborn, gestational age 23 completed weeks
P07.23	Extreme immaturity of newborn, gestational age 24 completed weeks
P07.24	Extreme immaturity of newborn, gestational age 25 completed weeks
P07.25	Extreme immaturity of newborn, gestational age 26 completed weeks
P07.26	Extreme immaturity of newborn, gestational age 27 completed weeks
P07.31	Preterm newborn, gestational age 28 completed weeks
P07.32	Preterm newborn, gestational age 29 completed weeks
P07.33	Preterm newborn, gestational age 30 completed weeks
P07.34	Preterm newborn, gestational age 31 completed weeks
P07.35	Preterm newborn, gestational age 32 completed weeks
P07.36	Preterm newborn, gestational age 33 completed weeks
P07.37	Preterm newborn, gestational age 34 completed weeks
P07.38	Preterm newborn, gestational age 35 completed weeks
P07.39	Preterm newborn, gestational age 36 completed weeks
b. Codes indicating extreme prematurity	
ICD-9 code	Definition
765	Disorders relating to extreme immaturity of infant
765.00	Extreme immaturity, unspecified [weight]
765.01	Extreme immaturity, less than 500 grams
765.02	Extreme immaturity, 500-749 grams

Appendix A: Codes

765.03	Extreme immaturity, 750-999 grams
765.04	Extreme immaturity, 1,000-1,249 grams
765.05	Extreme immaturity, 1,250-1,499 grams
765.06	Extreme immaturity, 1,500-1,749 grams
765.07	Extreme immaturity, 1,750-1,999 grams
765.08	Extreme immaturity, 2,000-2,499 grams
ICD-10 code	Definition
P07.2	Extreme immaturity of newborn
P07.20	Extreme immaturity of newborn, unspecified weeks of gestation
O42.012	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, second trimester
c. Other preterm codes	
ICD-9 code	Definition
765.1	Disorders relating to other preterm infants
765.10	Other preterm infants, unspecified [weight]
765.11	Other preterm infants, less than 500 grams
765.12	Other preterm infants, 500-749 grams
765.13	Other preterm infants, 750-999 grams
765.14	Other preterm infants, 1,000-1,249 grams
765.15	Other preterm infants, 1,250-1,499 grams
765.16	Other preterm infants, 1,500-1,749 grams
765.17	Other preterm infants, 1,750-1,999 grams
765.18	Other preterm infants, 2,000-2,499 grams
644.21	Onset of delivery before 37 completed weeks of gestation
ICD-10 code	Definition
P05.01	Disorders of newborn related to slow fetal growth and fetal malnutrition less than 500 grams
P05.02	Disorders of newborn related to slow fetal growth and fetal malnutrition, 500-749 grams
P05.03	Disorders of newborn related to slow fetal growth and fetal malnutrition, 750-999 grams
P05.04	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1000-1249 grams
P05.05	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1250-1499 grams
P05.06	Disorders of newborn related to slow fetal growth and fetal malnutrition, 1500-1749 grams
P05.11	Newborn small for gestational age, less than 500 grams
P05.12	Newborn small for gestational age, 500-749 grams
P05.13	Newborn small for gestational age, 750-999 grams
P05.14	Newborn small for gestational age, 1000-1249 grams
P05.15	Newborn small for gestational age, 1250-1499 grams
P05.16	Newborn small for gestational age, 1500-1749 grams
P07.01	Extremely low birth weight newborn, less than 500 grams
P07.02	Extremely low birth weight newborn, 500-749 grams
P07.03	Extremely low birth weight newborn, 750-999 grams
P07.14	Other low birth weight newborn,1000-1249 grams
P07.15	Other low birth weight newborn,1250-1499 grams
P07.16	Other low birth weight newborn,1500-1749 grams
P07.3	Preterm [premature] newborn [other]
P07.30	Preterm newborn, unspecified weeks of gestation
O60.1	Preterm labor with preterm delivery
O42.01	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture
O42.019	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, unspecified trimester
O42.013	Preterm premature rupture of membranes, onset of labor within 24 hours of rupture, third trimester
Other Codes	Description
ICD-9	
644.2	early onset of delivery
644.2	Early onset of delivery, unspecified as to episode of care or not applicable
644.21	Early onset of delivery, delivered, with or without mention of antepartum condition
776.6	anemia of prematurity
362.2	retinopathy of prematurity, unspecified
362.22	retinopathy of prematurity, stage 0
362.23	retinopathy of prematurity, stage 1
362.24	retinopathy of prematurity, stage 2
362.25	retinopathy of prematurity, stage 3
362.26	retinopathy of prematurity, stage 4
362.27	retinopathy of prematurity, stage 5
CPT	
49491	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
49492	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
67229	treatment of extensive or progressive retinopathy, 1 or more sessions; preterm infant (less than 37 weeks gestation at birth), performed from
836	anesthesia for hernia repairs in the lower abdomen not otherwise specified, infants younger than 37 weeks gestational age at birth
ICD-10 code	Definition
H35.1	Retinopathy of prematurity
P61.2	Anemia of prematurity
2. Multiple Gestation (V for ICD-9 and Z for ICD-10 codes excluded)	
ICD9 Code	Description
V27.2	Twins both liveborn
V27.3	Mother with twins one liveborn and one stillborn
V27.4	Mother with twins both stillborn
V27.5	Other multiple birth, all liveborn
V27.6	Other multiple birth, some liveborn
V31	Twin, mate liveborn
V32	Twin birth mate stillborn
V33	Twin, unspecified
V34	Other multiple, mates all liveborn
V35	Other multiple birth (three or more) mates all stillborn
V36	Other multiple, mates live- and stillborn
V37	Other multiple, unspecified

Appendix A: Codes

651	Multiple gestation
651.0x	Twin Pregnancy
651.1x	Triplet pregnancy
651.2x	Quadruplet pregnancy
651.3x	Twin pregnancy with fetal loss and retention of one fetus
651.4x	Triplet pregnancy with fetal loss and retention of one or more fetus(es)
651.5x	Quadruplet pregnancy with fetal loss and retention of one or more fetus(es)
651.6x	Other multiple pregnancy with fetal loss and retention of one or more fetus(es)
651.7x	Multiple gestation following (elective) fetal reduction
651.8x	Other specified multiple gestation
651.9x	Unspecified multiple gestation
652.6x	Multiple gestation with malpresentation of one fetus or more
660.5x	Locked Twins
662.3x	Delayed delivery of second twin, triplet, etc.
761.5x	Multiple pregnancy
ICD10 Code	Description
O30xxxx	Multiple gestation
O31xxxx	Complications specific to multiple gestation
O43.02	Fetus-to-fetus placental transfusion syndrome
O63.2	Delayed delivery of second twin, triplet, etc.
Z37.2	Twins, both liveborn
Z37.3	Twins, one liveborn and one stillborn
Z37.5	Other multiple births, all liveborn
Z37.50	Multiple births, unspecified, all liveborn
Z37.51	Triplets, all liveborn
Z37.52	Quadruplets, all liveborn
Z37.53	Quintuplets, all liveborn
Z37.54	Sextuplets, all liveborn
Z37.59	Other multiple births, all liveborn
Z37.6	Other multiple births, some liveborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z38.3	Twin liveborn infant, born in hospital
Z38.30	Twin liveborn infant, delivered vaginally
Z38.31	Twin liveborn infant, delivered by cesarean
Z38.4	Twin liveborn infant, born outside hospital
Z38.5	Twin liveborn infant, unspecified as to place of birth
Z38.6	Other multiple liveborn infant, born in hospital
Z38.61	Triplet liveborn infant, delivered vaginally
Z38.62	Triplet liveborn infant, delivered by cesarean
Z38.63	Quadruplet liveborn infant, delivered vaginally
Z38.64	Quadruplet liveborn infant, delivered by cesarean
Z38.65	Quintuplet liveborn infant, delivered vaginally
Z38.66	Quintuplet liveborn infant, delivered by cesarean
Z38.68	Other multiple liveborn infant, delivered vaginally
Z38.69	Other multiple liveborn infant, delivered by cesarean
Z38.7	Other multiple liveborn infant, born outside hospital
Z38.8	Other multiple liveborn infant, unspecified as to place of birth
P01.5	Newborn affected by multiple pregnancy
3. Post-Term Codes	
ICD-9 code	Definition
645	Late Pregnancy
645.1	Post term pregnancy
645.1	Post term pregnancy, unspecified as to episode of care or not applicable
645.11	Post term pregnancy, delivered, with or without mention of antepartum condition
645.13	Post term pregnancy, antepartum condition or complication
645.2	Prolonged pregnancy
645.2	Prolonged pregnancy, unspecified as to episode of care or not applicable
645.21	Prolonged pregnancy, delivered, with or without mention of antepartum condition
645.23	Prolonged pregnancy, antepartum condition or complication
766.2	Late infant, not 'heavy-for-dates'
766.21	Post-term infant
766.22	Prolonged gestation of infant
ICD-10 code	Definition
O48	Late pregnancy
O48.0	Post-term pregnancy
O48.1	Prolonged pregnancy
P08.2	Late newborn, not heavy for gestational age
P08.21	Post-term newborn
P08.22	Prolonged gestation of newborn
Z3A.41	41 weeks gestation of pregnancy
Z3A.42	42 weeks gestation of pregnancy
Z3A.49	Greater than 42 weeks gestation of pregnancy
4. Codes indicating a prenatal care visit:	
ICD-9: V220x, V221x, V23xx	
ICD-10: O0900, O0901, O0902, O0903, O0910, O0911, O0912, O0913, O09211, O09212, O09213, O09219, O09291, O09292, O09293, O09299, O0930, O0931, O0932, O0933, O0940, O0941, O0942, O0943, O09511, O09512, O09513, O09519, O09521, O09522, O09523, O09529, O09611, O09612, O09613, O09619, O09621, O09622, O09623, O09629, O0970, O0971, O0972, O0973, O09811, O09812, O09813, O09819, O09821, O09822, O09823, O09829, O09891, O09892, O09893, O09899, O0990, O0991, O0992, O0993, O09A0, O09A1, O09A2, O09A3, O3680X0, O3680X1, O3680X2, O3680X3, O3680X4, O3680X5, O3680X9, Z3400, Z3401, Z3402, Z3403, Z3480, Z3481, Z3482, Z3483, Z3490, Z3491, Z3492, Z3493, Z362	

Appendix A: Codes

Other anti-diabetic treatments (other than insulin)
1st Generation SUs
ACETOHEXAMIDE
TOLBUTAMIDE
TOLAZAMIDE
CHLORPROPAMIDE
AGIs
ACARBOSE
MIGLITOL
Glitazones
ALOGLIPTIN BENZOATE/PIOGLITAZONE HCL
PIOGLITAZONE HCL
PIOGLITAZONE HCL/GLIMEPIRIDE
PIOGLITAZONE HCL/METFORMIN HCL
ROSIGLITAZONE MALEATE
ROSIGLITAZONE MALEATE/GLIMEPIRIDE
ROSIGLITAZONE MALEATE/METFORMIN HCL
Meglitinides
NATEGLINIDE
REPAGLINIDE
REPAGLINIDE/METFORMIN HCL
GLP-1 RA
SEMAGLUTIDE (admin.: oral)
Insulin
Bolus insulins
INSULIN GLULISINE
INSULIN REGULAR,BEEF-PORK
INSULIN ASPART (NIACINAMIDE)
INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT
INSULIN REGULAR,HUMAN BUFFERED
INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT/CHAMBER/INHALER
INSULIN ASPART
INSULIN ASPART PROTAMINE HUMAN/INSULIN ASPART
INSULIN LISPRO PROTAMINE AND INSULIN LISPRO
INSULIN LISPRO
INSULIN REGULAR, HUMAN
Intermediate and Long-acting Insulins
INSULIN DEGLUDEC
INSULIN DETEMIR
INSULIN DEGLUDEC/LIRAGLUTIDE
INSULIN NPH HUMAN AND INSULIN REGULAR HUMAN SEMI-SYNTHETIC
INSULIN NPH HUMAN SEMI-SYNTHETIC
INSULIN ISOPHANE NPH,BF-PK
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG/LIXISENATIDE
INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG
INSULIN NPH HUMAN ISOPHANE
INSULIN NPH HUMAN ISOPHANE/INSULIN REGULAR, HUMAN

Appendix B: Table 1

	Semaglutide vs Standard - Cohort ITT (12m +/- 90 days)						Semaglutide vs Standard - Cohort AT 12-30w					
	UNMATCHED			MATCHED			UNMATCHED			MATCHED		
Baseline characteristics	**Standard care (DPP-4i, SGLT-2i, SU)**	**Semaglutide**	**St. Diff**	**Standard care (DPP-4i, SGLT-2i, SU)**	**Semaglutide**	**St. Diff**	**Standard care (DPP-4i, SGLT-2i, SU)**	**Semaglutide**	**St. Diff**	**Standard care (DPP-4i, SGLT-2i, SU)**	**Semaglutide**	**St. Diff**
Number of patients	26,541	635		633	633		18,706	682		678	678	
Demographics												
Year of Cohort Entry Date												
...5 Dec 2017 - 31 Dec 2018; n (%)	10,159 (38.3%)	8 (1.3%)	1.05	36 (5.7%)	8 (1.3%)	0.00	6,145 (32.9%)	5 (0.7%)	0.95	4 (0.6%)	5 (0.7%)	0.00
...1 Jan 2019 - 31 Dec 2019; n (%)	9,948 (37.5%)	307 (48.3%)	-0.22	228 (36.0%)	306 (48.3%)	-0.25	6,058 (32.4%)	253 (37.1%)	-0.10	262 (38.6%)	252 (37.2%)	0.03
...1 Jan 2020 - 31 Dec 2020; n (%)	6,434 (24.2%)	320 (50.4%)	-0.56	369 (58.3%)	319 (50.4%)	0.16	5,978 (32.0%)	384 (56.3%)	-0.50	382 (56.3%)	382 (56.3%)	0.00
...1 Jan 2021 -30 Jun 2021; n (%)	0 (0.0%)	0 (0.0%)	0.00	0 (0.0%)	0 (0.0%)	0.00	525 (2.8%)	40 (5.9%)	-0.15	30 (4.4%)	39 (5.8%)	-0.06
Quarter Calendar Time Score												
...mean (sd)	4.39 (2.32)	6.35 (1.36)	-1.03	6.41 (1.66)	6.34 (1.36)	0.05	4.34 (2.67)	6.30 (1.70)	-0.88	6.16 (1.77)	6.30 (1.70)	-0.08
...median [IQR]	4.00 [2.00, 6.00]	7.00 [5.00, 7.00]	--	7.00 [5.00, 8.00]	7.00 [5.00, 7.00]	--	4.35 [1.86, 6.62]	6.46 [5.00, 7.66]	--	6.33 [4.63, 7.62]	6.45 [5.00, 7.66]	--
Age*												
...mean (sd)	64.75 (11.55)	56.80 (11.95)	0.68	56.59 (11.98)	56.85 (11.94)	-0.02	65.27 (11.34)	56.87 (11.91)	0.72	56.40 (11.71)	56.95 (11.87)	-0.05
...median [IQR]	67.00 [58.00, 73.00]	57.00 [48.00, 67.00]	--	57.00 [48.00, 66.00]	57.00 [48.00, 67.00]	--	67.00 [59.00, 73.00]	57.00 [48.00, 66.00]	--	57.00 [48.00, 66.00]	57.00 [48.00, 66.00]	--
Age squared*												
...mean (sd)	777,625.01 (255,648.88)	603,932.18 (240,773.04)	0.70	595,923.84 (245,993.22)	604,345.50 (240,737.59)	-0.03	788,645.31 (252,226.56)	605,313.19 (240,904.21)	0.74	595,304.40 (232,661.95)	606,900.52 (240,515.39)	-0.05
...median [IQR]	812,509.00 [591,116.50, 938,739.00]	588,069.00 [407,524.00, 794,155.00]	--	579,198.50 [401,895.25, 788,436.00]	588,069.00 [414,649.00, 794,254.75]	--	812,509.00 [617,776.00, 951,934.00]	587,165.00 [417,024.00, 788,436.00]	--	586,035.00 [417,024.00, 771,045.75]	588,069.00 [417,024.00, 788,436.00]	--
Age Categories												
...18 - 40; n (%)	931 (3.5%)	66 (10.4%)	-0.27	62 (9.8%)	65 (10.3%)	-0.02	624 (3.3%)	66 (9.7%)	-0.26	73 (10.8%)	64 (9.4%)	0.05
...41 - 50; n (%)	2,528 (9.5%)	131 (20.6%)	-0.31	143 (22.6%)	130 (20.5%)	0.05	1,618 (8.6%)	138 (20.2%)	-0.34	134 (19.8%)	138 (20.4%)	-0.01
...51 - 60; n (%)	4,784 (18.0%)	192 (30.2%)	-0.29	174 (27.5%)	192 (30.3%)	-0.06	3,113 (16.6%)	207 (30.4%)	-0.33	191 (28.2%)	205 (30.2%)	-0.04
...61 - 70; n (%)	9,434 (35.5%)	159 (25.0%)	0.23	169 (26.7%)	159 (25.1%)	0.04	6,907 (36.9%)	180 (26.4%)	0.23	205 (30.2%)	180 (26.5%)	0.08
...71 - 80; n (%)	8,864 (33.4%)	87 (13.7%)	0.48	85 (13.4%)	87 (13.7%)	-0.01	6,444 (34.4%)	91 (13.3%)	0.51	75 (11.1%)	91 (13.4%)	-0.07
Sex*												
...Male; n (%)	14,310 (53.9%)	302 (47.6%)	0.13	305 (48.2%)	301 (47.6%)	0.01	10,545 (56.4%)	331 (48.5%)	0.16	316 (46.6%)	330 (48.7%)	-0.04
...Female; n (%)	12,231 (46.1%)	333 (52.4%)	-0.13	328 (51.8%)	332 (52.4%)	-0.01	8,161 (43.6%)	351 (51.5%)	-0.16	362 (53.4%)	348 (51.3%)	0.04
Race categories*												
...White; n (%)	13,684 (51.6%)	384 (60.5%)	-0.18	381 (60.2%)	382 (60.3%)	0.00	9,817 (52.5%)	437 (64.1%)	-0.24	435 (64.2%)	433 (63.9%)	0.01
...Not White; n (%)	12,857 (48.4%)	251 (39.5%)	0.18	252 (39.8%)	251 (39.7%)	0.00	8,889 (47.5%)	245 (35.9%)	0.24	243 (35.8%)	245 (36.1%)	-0.01
Combined comorbidity score, 180 days*												
...mean (sd)	2.64 (1.89)	2.30 (1.59)	0.19	2.25 (1.63)	2.29 (1.59)	-0.02	2.59 (1.88)	2.28 (1.62)	0.18	2.30 (1.76)	2.26 (1.62)	0.02
...median [IQR]	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	--	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	--	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	--	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	--
Frailty score*												
...Robust; n (%)	6,605 (24.9%)	195 (30.7%)	-0.13	205 (32.4%)	195 (30.8%)	0.03	4,934 (26.4%)	191 (28.0%)	-0.04	184 (27.1%)	190 (28.0%)	-0.02
...Pre-frail; n (%)	9,985 (37.6%)	233 (36.7%)	0.02	235 (37.1%)	232 (36.7%)	0.01	7,092 (37.9%)	260 (38.1%)	0.00	246 (36.3%)	258 (38.1%)	-0.04
...Frail; n (%)	9,951 (37.5%)	207 (32.6%)	0.10	193 (30.5%)	206 (32.5%)	-0.04	6,680 (35.7%)	231 (33.9%)	0.04	248 (36.6%)	230 (33.9%)	0.06
HbA1c test order (Number of tests)*												

Appendix B: Table 1

...mean (sd)	8.61 (1.49)	8.67 (1.59)	-0.04	8.77 (1.60)	8.67 (1.59)	0.06	8.53 (1.43)	8.62 (1.51)	-0.06	8.63 (1.46)	8.63 (1.51)	0.00
...median [IQR]	8.20 [7.50, 9.30]	8.10 [7.50, 9.50]	--	8.30 [7.60, 9.60]	8.10 [7.50, 9.50]	--	8.10 [7.50, 9.10]	8.20 [7.50, 9.40]	--	8.20 [7.60, 9.20]	8.20 [7.50, 9.40]	--
Smoking; n (%)*	3,381 (12.7%)	80 (12.6%)	0.00	73 (11.5%)	78 (12.3%)	-0.02	2,379 (12.7%)	89 (13.0%)	-0.01	99 (14.6%)	88 (13.0%)	0.05
Obesity or overweight; n (%)*	10,389 (39.1%)	325 (51.2%)	-0.24	309 (48.8%)	323 (51.0%)	-0.04	7,030 (37.6%)	334 (49.0%)	-0.23	323 (47.6%)	331 (48.8%)	-0.02
Overweight; n (%)	8,087 (30.5%)	279 (43.9%)	-0.28	256 (40.4%)	277 (43.8%)	-0.07	5,420 (29.0%)	294 (43.1%)	-0.30	264 (38.9%)	291 (42.9%)	-0.08
Obesity; n (%)	2,798 (10.5%)	55 (8.7%)	0.06	64 (10.1%)	55 (8.7%)	0.05	1,930 (10.3%)	53 (7.8%)	0.09	67 (9.9%)	53 (7.8%)	0.07
Cardiovascular Comorbidities												
Hypertension; n (%)*	5,002 (18.8%)	153 (24.1%)	-0.13	138 (21.8%)	151 (23.9%)	-0.05	3,743 (20.0%)	159 (23.3%)	-0.08	154 (22.7%)	158 (23.3%)	-0.01
Hyperlipidemia; n (%)*	18,366 (69.2%)	451 (71.0%)	-0.04	435 (68.7%)	450 (71.1%)	-0.05	12,913 (69.0%)	467 (68.5%)	0.01	450 (66.4%)	465 (68.6%)	-0.05
Atherosclerosis Cardiovascular Disease; n (%)*	5,336 (20.1%)	93 (14.6%)	0.15	82 (13.0%)	92 (14.5%)	-0.04	3,696 (19.8%)	95 (13.9%)	0.16	90 (13.3%)	94 (13.9%)	-0.02
Old MI; n (%)	608 (2.3%)	8 (1.3%)	0.08	13 (2.1%)	8 (1.3%)	0.06	432 (2.3%)	13 (1.9%)	0.03	11 (1.6%)	13 (1.9%)	-0.02
Acute MI ; n (%)	195 (0.7%)	8 (1.3%)	-0.06	5 (0.8%)	8 (1.3%)	-0.05	126 (0.7%)	5 (0.7%)	0.00	2 (0.3%)	5 (0.7%)	-0.06
ACS/unstable angina; n (%)	269 (1.0%)	7 (1.1%)	-0.01	6 (0.9%)	7 (1.1%)	-0.02	172 (0.9%)	5 (0.7%)	0.02	6 (0.9%)	5 (0.7%)	0.02
Stable angina; n (%)	934 (3.5%)	24 (3.8%)	-0.02	18 (2.8%)	24 (3.8%)	-0.06	611 (3.3%)	22 (3.2%)	0.01	22 (3.2%)	22 (3.2%)	0.00
CAD and other forms of chronic ischemic heart disease; n (%)	3,768 (14.2%)	61 (9.6%)	0.14	57 (9.0%)	61 (9.6%)	-0.02	2,628 (14.0%)	68 (10.0%)	0.12	67 (9.9%)	68 (10.0%)	0.00
History of CABG or PTCA ; n (%)	1,086 (4.1%)	18 (2.8%)	0.07	16 (2.5%)	18 (2.8%)	-0.02	746 (4.0%)	21 (3.1%)	0.05	18 (2.7%)	21 (3.1%)	-0.02
PAD or PAD surgery; n (%)	1,792 (6.8%)	33 (5.2%)	0.07	21 (3.3%)	32 (5.1%)	-0.09	1,200 (6.4%)	29 (4.3%)	0.09	23 (3.4%)	28 (4.1%)	-0.04
Cerebrovascular disease; n (%)*	723 (2.7%)	11 (1.7%)	0.07	6 (0.9%)	11 (1.7%)	-0.07	517 (2.8%)	15 (2.2%)	0.04	12 (1.8%)	15 (2.2%)	-0.03
Stroke (Ischemic or hemorrhagic); n (%)	433 (1.6%)	8 (1.3%)	0.03	2 (0.3%)	8 (1.19%)	-0.10	300 (1.6%)	9 (1.3%)	0.03	9 (1.3%)	9 (1.3%)	0.00
TIA; n (%)	255 (1.0%)	3 (0.5%)	0.06	2 (0.3%)	3 (0.5%)	-0.03	171 (0.9%)	7 (1.0%)	-0.01	3 (0.4%)	7 (1.0%)	-0.07
Late effects of cerebrovascular disease; n (%)	252 (0.9%)	4 (0.6%)	0.03	3 (0.5%)	4 (0.6%)	-0.01	175 (0.9%)	5 (0.7%)	0.02	3 (0.4%)	5 (0.7%)	-0.04
Heart Failure; n (%)*	1,508 (5.7%)	21 (3.3%)	0.12	14 (2.2%)	20 (3.2%)	-0.06	1,033 (5.5%)	24 (3.5%)	0.10	24 (3.5%)	22 (3.2%)	0.02
Atrial fibrillation; n (%)*	1,541 (5.8%)	22 (3.5%)	0.11	24 (3.8%)	21 (3.3%)	0.03	1,132 (6.1%)	27 (4.0%)	0.10	26 (3.8%)	25 (3.7%)	0.01
Other cardiac dysrhythmia; n (%)	2,486 (9.4%)	38 (6.0%)	0.13	39 (6.2%)	37 (5.8%)	0.02	1,760 (9.4%)	48 (7.0%)	0.09	48 (7.1%)	46 (6.8%)	0.01
Diabetes Mellitus Comorbidities												
Diabetic nephropathy; n (%)*	4,503 (17.0%)	68 (10.7%)	0.18	60 (9.5%)	68 (10.7%)	-0.04	2,999 (16.0%)	78 (11.4%)	0.13	74 (10.9%)	78 (11.5%)	-0.02
Diabetic neuropathy; n (%)*	5,402 (20.4%)	95 (15.0%)	0.14	86 (13.6%)	95 (15.0%)	-0.04	3,492 (18.7%)	107 (15.7%)	0.08	103 (15.2%)	107 (15.8%)	-0.02
Diabetic retinopathy ; n (%)*	1,550 (5.8%)	38 (6.0%)	-0.01	44 (7.0%)	38 (6.0%)	0.04	949 (5.1%)	33 (4.8%)	0.01	30 (4.4%)	33 (4.9%)	-0.02
Diabetes with unspecified complications; n (%)*	1,628 (6.1%)	41 (6.5%)	-0.02	45 (7.1%)	40 (6.3%)	0.03	1,088 (5.8%)	46 (6.7%)	-0.04	39 (5.8%)	46 (6.8%)	-0.04
Diabetes with peripheral circulatory disorders, amputations, and diabetic foot; n (%)*	413 (1.6%)	10 (1.6%)	0.00	10 (1.6%)	9 (1.4%)	0.02	303 (1.6%)	10 (1.5%)	0.01	11 (1.6%)	10 (1.5%)	0.01
Diabetes with peripheral circulatory disorders; n (%)	47 (0.2%)	1 (0.2%)	0.00	2 (0.3%)	1 (0.2%)	0.02	34 (0.2%)	1 (0.1%)	0.03	1 (0.1%)	1 (0.1%)	0.00
Lower-limb amputations; n (%)	106 (0.4%)	1 (0.2%)	0.04	2 (0.3%)	1 (0.2%)	0.02	71 (0.4%)	1 (0.1%)	0.06	0 (0.0%)	1 (0.1%)	-0.04
Diabetic Foot; n (%)	303 (1.1%)	9 (1.4%)	-0.03	7 (1.1%)	8 (1.3%)	-0.02	224 (1.2%)	9 (1.3%)	-0.01	10 (1.5%)	9 (1.3%)	0.02
Renal Comorbidities												
Chronic kidney disease (CKD); n (%)	3,910 (14.7%)	64 (10.1%)	0.14	62 (9.8%)	64 (10.1%)	-0.01	2,581 (13.8%)	64 (9.4%)	0.14	57 (8.4%)	64 (9.4%)	-0.04
CKD Stage 1-2; n (%)*	1,558 (5.9%)	20 (3.1%)	0.14	13 (2.1%)	20 (3.2%)	-0.07	1,040 (5.6%)	18 (2.6%)	0.15	18 (2.7%)	18 (2.7%)	0.00
CKD Stage 3-4; n (%)*	2,363 (8.9%)	46 (7.2%)	0.06	49 (7.7%)	46 (7.3%)	0.02	1,560 (8.3%)	47 (6.9%)	0.05	41 (6.0%)	47 (6.9%)	-0.04
CKD unspecified ; n (%)*	484 (1.8%)	7 (1.1%)	0.06	10 (1.6%)	7 (1.1%)	0.04	311 (1.7%)	8 (1.2%)	0.04	9 (1.3%)	8 (1.2%)	0.01
Miscellaneous renal disease; n (%)	1,100 (4.1%)	22 (3.5%)	0.03	21 (3.3%)	22 (3.5%)	-0.01	764 (4.1%)	25 (3.7%)	0.02	17 (2.5%)	25 (3.7%)	-0.07
Other Comorbidities												
Mood disorders; n (%)*	3,392 (12.8%)	90 (14.2%)	-0.04	79 (12.5%)	90 (14.2%)	-0.05	2,272 (12.1%)	105 (15.4%)	-0.10	107 (15.8%)	105 (15.5%)	0.01

Appendix B: Table 1

Anxiety; n (%)	2,497 (9.4%)	68 (10.7%)	-0.04	61 (9.6%)	68 (10.7%)	-0.04	1,681 (9.0%)	74 (10.9%)	-0.06	85 (12.5%)	74 (10.9%)	0.05
Depression; n (%)	1,505 (5.7%)	41 (6.5%)	-0.03	35 (5.5%)	41 (6.5%)	-0.04	1,002 (5.4%)	54 (7.9%)	-0.10	50 (7.4%)	54 (8.0%)	-0.02
Obstructive sleep apnea; n (%)*	3,293 (12.4%)	125 (19.7%)	-0.20	116 (18.3%)	124 (19.6%)	-0.03	2,238 (12.0%)	138 (20.2%)	-0.22	139 (20.5%)	137 (20.2%)	0.01
COPD; n (%)*	2,166 (8.2%)	38 (6.0%)	0.09	39 (6.2%)	38 (6.0%)	0.01	1,525 (8.2%)	39 (5.7%)	0.10	44 (6.5%)	39 (5.8%)	0.03
Asthma; n (%)*	1,496 (5.6%)	48 (7.6%)	-0.08	47 (7.4%)	48 (7.6%)	-0.01	1,018 (5.4%)	58 (8.5%)	-0.12	58 (8.6%)	57 (8.4%)	0.01
Osteoarthrosis; n (%)*	3,851 (14.5%)	100 (15.7%)	-0.03	102 (16.1%)	99 (15.6%)	0.01	2,674 (14.3%)	109 (16.0%)	-0.05	106 (15.6%)	109 (16.1%)	-0.01
NASH/NAFLD; n (%)*	1,418 (5.3%)	48 (7.6%)	-0.09	49 (7.7%)	48 (7.6%)	0.00	952 (5.1%)	50 (7.3%)	-0.09	58 (8.6%)	50 (7.4%)	0.04
Medications use												
Antihypertensive medications; n (%)*	21,939 (82.7%)	491 (77.3%)	0.14	471 (74.4%)	489 (77.3%)	-0.07	15,621 (83.5%)	532 (78.0%)	0.14	519 (76.5%)	529 (78.0%)	-0.04
ACEi/ARBs; n (%)	18,865 (71.1%)	421 (66.3%)	0.10	407 (64.3%)	420 (66.4%)	-0.04	13,406 (71.7%)	454 (66.6%)	0.11	450 (66.4%)	451 (66.5%)	0.00
Beta blockers; n (%)	8,403 (31.7%)	168 (26.5%)	0.11	168 (26.5%)	167 (26.4%)	0.00	6,077 (32.5%)	197 (28.9%)	0.08	177 (26.1%)	195 (28.8%)	-0.06
Calcium channel blockers; n (%)	7,033 (26.5%)	149 (23.5%)	0.07	143 (22.6%)	147 (23.2%)	-0.01	5,063 (27.1%)	165 (24.2%)	0.07	128 (18.9%)	164 (24.2%)	-0.13
Thiazide; n (%)	3,407 (12.8%)	79 (12.4%)	0.01	76 (12.0%)	79 (12.5%)	-0.02	2,554 (13.7%)	90 (13.2%)	0.01	102 (15.0%)	90 (13.3%)	0.05
Diuretics; n (%)	9,567 (36.0%)	213 (33.5%)	0.05	203 (32.1%)	212 (33.5%)	-0.03	6,838 (36.6%)	241 (35.3%)	0.03	234 (34.5%)	240 (35.4%)	-0.02
Statins Other lipid-lowering drugs; n (%)*	20,202 (76.1%)	467 (73.5%)	0.06	460 (72.7%)	466 (73.6%)	-0.02	14,641 (78.3%)	487 (71.4%)	0.16	466 (68.7%)	485 (71.5%)	-0.06
Statins; n (%)	19,449 (73.3%)	454 (71.5%)	0.04	445 (70.3%)	453 (71.6%)	-0.03	14,094 (75.3%)	473 (69.4%)	0.13	453 (66.8%)	471 (69.5%)	-0.06
Other lipid-lowering drugs; n (%)	2,441 (9.2%)	56 (8.8%)	0.01	60 (9.5%)	56 (8.8%)	0.02	1,749 (9.3%)	54 (7.9%)	0.05	68 (10.0%)	54 (8.0%)	0.07
Opioids; n (%)*	4,279 (16.1%)	104 (16.4%)	-0.01	110 (17.4%)	104 (16.4%)	0.03	2,813 (15.0%)	110 (16.1%)	-0.03	119 (17.6%)	109 (16.1%)	0.04
Mood Stabilizing Medications; n (%)*	7,564 (28.5%)	232 (36.5%)	-0.17	219 (34.6%)	231 (36.5%)	-0.04	5,192 (27.8%)	258 (37.8%)	-0.21	257 (37.9%)	258 (38.1%)	0.00
Antidepressants; n (%)	6,079 (22.9%)	202 (31.8%)	-0.20	181 (28.6%)	201 (31.8%)	-0.07	4,180 (22.3%)	219 (32.1%)	-0.22	211 (31.1%)	219 (32.3%)	-0.03
Anxiolytics/hypnotics; n (%)	1,244 (4.7%)	26 (4.1%)	0.03	34 (5.4%)	26 (4.1%)	0.06	848 (4.5%)	39 (5.7%)	-0.05	54 (8.0%)	39 (5.8%)	0.09
Benzodiazepine; n (%)	2,202 (8.3%)	49 (7.7%)	0.02	54 (8.5%)	49 (7.7%)	0.03	1,487 (7.9%)	59 (8.7%)	-0.03	76 (11.2%)	59 (8.7%)	0.08
Gabapentinoids; n (%)*	3,592 (13.5%)	74 (11.7%)	0.05	73 (11.5%)	73 (11.5%)	0.00	2,426 (13.0%)	89 (13.0%)	0.00	80 (11.8%)	89 (13.1%)	-0.04
Health care utilization indicators												
Number of medication claims*												
...mean (sd)	11.01 (7.05)	12.03 (7.40)	-0.14	11.54 (7.20)	12.00 (7.38)	-0.06	10.98 (6.96)	12.34 (7.31)	-0.19	12.70 (8.53)	12.32 (7.31)	0.05
...median [IQR]	9.00 [6.00, 14.00]	10.00 [7.00, 15.00]	--	10.00 [6.00, 15.00]	10.00 [7.00, 15.00]	--	9.00 [6.00, 14.00]	11.00 [7.00, 16.00]	--	11.00 [7.00, 16.00]	11.00 [7.00, 16.00]	--
Number of office visits*												
...mean (sd)	5.63 (4.61)	5.78 (4.53)	-0.03	5.76 (4.81)	5.76 (4.51)	0.00	5.47 (4.67)	5.75 (4.25)	-0.06	5.89 (5.06)	5.71 (4.24)	0.04
...median [IQR]	4.00 [3.00, 7.00]	5.00 [3.00, 7.00]	--	5.00 [3.00, 7.00]	5.00 [3.00, 7.00]	--	4.00 [3.00, 7.00]	5.00 [3.00, 7.00]	--	4.00 [3.00, 7.00]	5.00 [3.00, 7.00]	--
Number of hospitalizations/ED visit (binary)*												
...mean (sd)	0.39 (1.24)	0.35 (1.00)	0.04	0.36 (1.11)	0.35 (1.00)	0.01	0.36 (1.35)	0.34 (1.00)	0.02	0.40 (1.16)	0.34 (1.00)	0.06
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--
Brand name prescription - unique value*												
...mean (sd)	9.19 (4.36)	9.62 (4.70)	-0.09	9.41 (4.69)	9.60 (4.69)	-0.04	9.11 (4.31)	9.53 (4.67)	-0.09	9.53 (5.13)	9.50 (4.65)	0.01
...median [IQR]	8.00 [6.00, 11.00]	9.00 [6.00, 12.00]	--	8.00 [6.00, 12.00]	9.00 [6.00, 12.00]	--	8.00 [6.00, 11.00]	9.00 [6.00, 12.00]	--	9.00 [6.00, 12.00]	9.00 [6.00, 12.00]	--
Generic name prescription - unique value*												
...mean (sd)	0.99 (0.03)	0.99 (0.04)	0.00	9.30 (4.64)	9.49 (4.61)	-0.04	9.04 (4.25)	9.41 (4.56)	-0.08	9.41 (5.03)	9.39 (4.55)	0.00
...median [IQR]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	--	8.00 [6.00, 11.00]	9.00 [6.00, 12.00]	--	8.00 [6.00, 11.00]	8.00 [6.00, 12.00]	--	8.00 [6.00, 12.00]	8.00 [6.00, 12.00]	--
Generic/Brand unique prescriptions												
...mean (sd)	0.99 (0.03)	0.99 (0.04)	0.00	0.99 (0.04)	0.99 (0.04)	0.00	0.99 (0.03)	0.99 (0.04)	0.00	0.99 (0.03)	0.99 (0.04)	0.00
...median [IQR]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	--	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	--	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	--	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	--
Number of Endocrinologist visits*												
...mean (sd)	0.12 (0.50)	0.28 (0.74)	-0.25	0.26 (0.77)	0.27 (0.72)	-0.01	0.08 (0.42)	0.27 (0.74)	-0.32	0.23 (0.77)	0.24 (0.62)	-0.01
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	--

Appendix B: Table 1

Number of HbA1c*												
...mean (sd)	1.58 (0.72)	1.62 (0.72)	-0.06	1.64 (0.67)	1.61 (0.72)	0.04		1.57 (0.70)	1.59 (0.69)	-0.03	1.55 (0.69)	1.59 (0.69)	-0.06
...median [IQR]	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	--	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	--		2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	--	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	--
Basic or comprehensive metabolic blood chemistry test; n (%)*	22,174 (83.5%)	500 (78.7%)	0.12	499 (78.8%)	498 (78.7%)	0.00		15,699 (83.9%)	546 (80.1%)	0.10	537 (79.2%)	542 (79.9%)	-0.02
Number of bone density tests; n (%)*	1,038 (3.9%)	24 (3.8%)	0.01	17 (2.7%)	24 (3.8%)	-0.06		716 (3.8%)	24 (3.5%)	0.02	28 (4.1%)	23 (3.4%)	0.04
PSA test or Prostate exam for DRE; n (%)*	5,109 (19.2%)	117 (18.4%)	0.02	113 (17.9%)	117 (18.5%)	-0.02		3,755 (20.1%)	124 (18.2%)	0.05	111 (16.4%)	124 (18.3%)	-0.05
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	1,245 (4.7%)	36 (5.7%)	-0.05	36 (5.7%)	36 (5.7%)	0.00		887 (4.7%)	43 (6.3%)	-0.07	40 (5.9%)	43 (6.3%)	-0.02
Number of Mammograms (Breast cancer screening); n (%)	3,308 (12.5%)	99 (15.6%)	-0.09	94 (14.8%)	99 (15.6%)	-0.02		2,180 (11.7%)	100 (14.7%)	-0.09	96 (14.2%)	99 (14.6%)	-0.01
Number of Pap smear (Cervical cancer screening); n (%)*	856 (3.2%)	38 (6.0%)	-0.13	37 (5.8%)	37 (5.8%)	0.00		533 (2.8%)	36 (5.3%)	-0.13	38 (5.6%)	35 (5.2%)	0.02
Flu vaccine; n (%)	4,932 (18.6%)	110 (17.3%)	0.03	90 (14.2%)	110 (17.4%)	-0.09		3,625 (19.4%)	136 (19.9%)	-0.01	124 (18.3%)	136 (20.1%)	-0.05
Pneumococcal vaccine; n (%)	6,982 (26.3%)	155 (24.4%)	0.04	150 (23.7%)	155 (24.5%)	-0.02		5,093 (27.2%)	189 (27.7%)	-0.01	191 (28.2%)	189 (27.9%)	0.01
Copay for pharmacy cost (charges in U.S. $)*													
...mean (sd)	200.93 (403.50)	296.02 (350.92)	-0.25	227.65 (399.41)	295.75 (351.08)	-0.18		189.00 (322.50)	280.00 (299.36)	-0.29	244.73 (382.68)	280.00 (299.65)	-0.10
...median [IQR]	119.08 [44.36, 256.47]	207.17 [101.87, 381.05]	--	134.85 [47.08, 298.01]	207.17 [101.91, 379.84]	--		107.26 [37.51, 239.55]	204.83 [99.90, 371.72]	--	141.41 [54.32, 289.05]	204.83 [99.90, 371.72]	--
Business type*													
...Commercial; n (%)	8,101 (30.5%)	374 (58.9%)	-0.60	372 (58.8%)	373 (58.9%)	0.00		5,441 (29.1%)	408 (59.8%)	-0.65	419 (61.8%)	404 (59.6%)	0.05
...Medicare; n (%)	18,440 (69.5%)	261 (41.1%)	0.60	261 (41.2%)	260 (41.1%)	0.00		13,265 (70.9%)	274 (40.2%)	0.65	259 (38.2%)	274 (40.4%)	-0.05
Low income indicator; n (%)*	3,690 (13.9%)	54 (8.5%)	0.17	64 (10.1%)	53 (8.4%)	0.06		2,769 (14.3%)	70 (9.4%)	0.15	58 (8.6%)	61 (9.0%)	-0.01

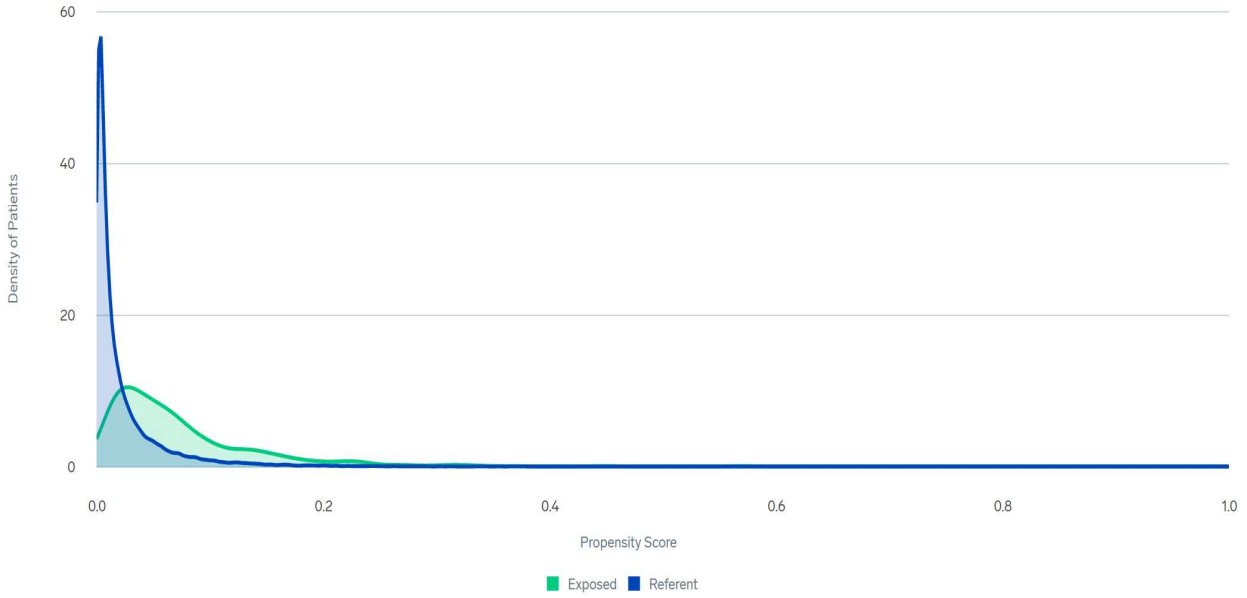
***variables included in the PS model**

Appendix B: Propensity

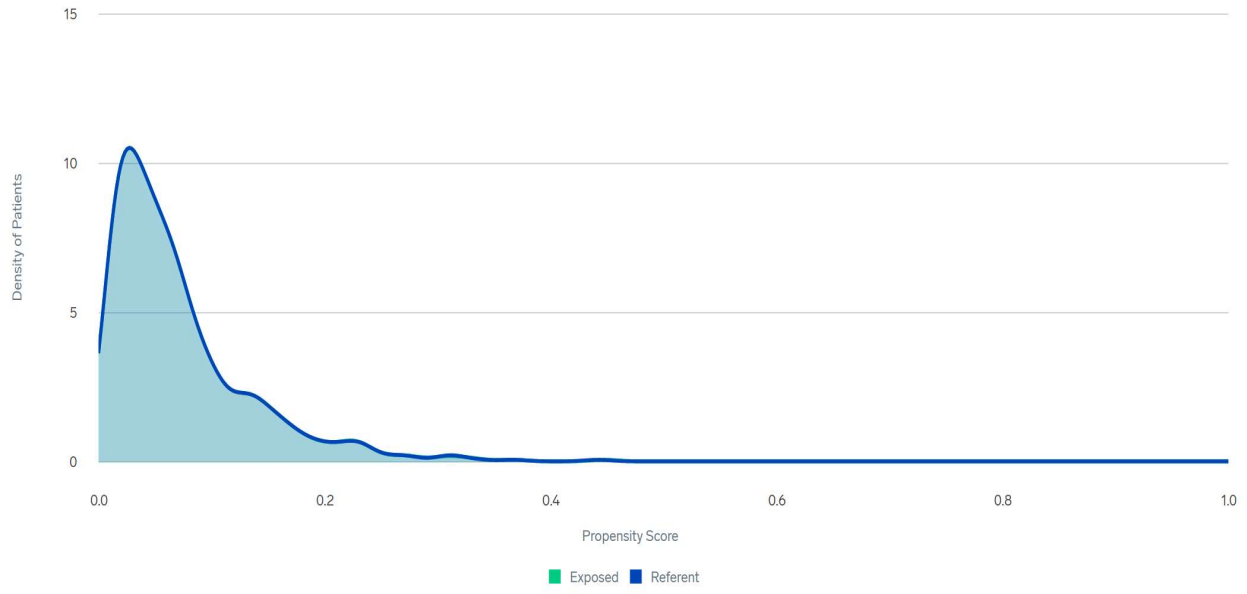
OPTUM

Semaglutide vs Standard - Cohort ITT (12m +/- 90 days)

BEFORE PS MATCHING



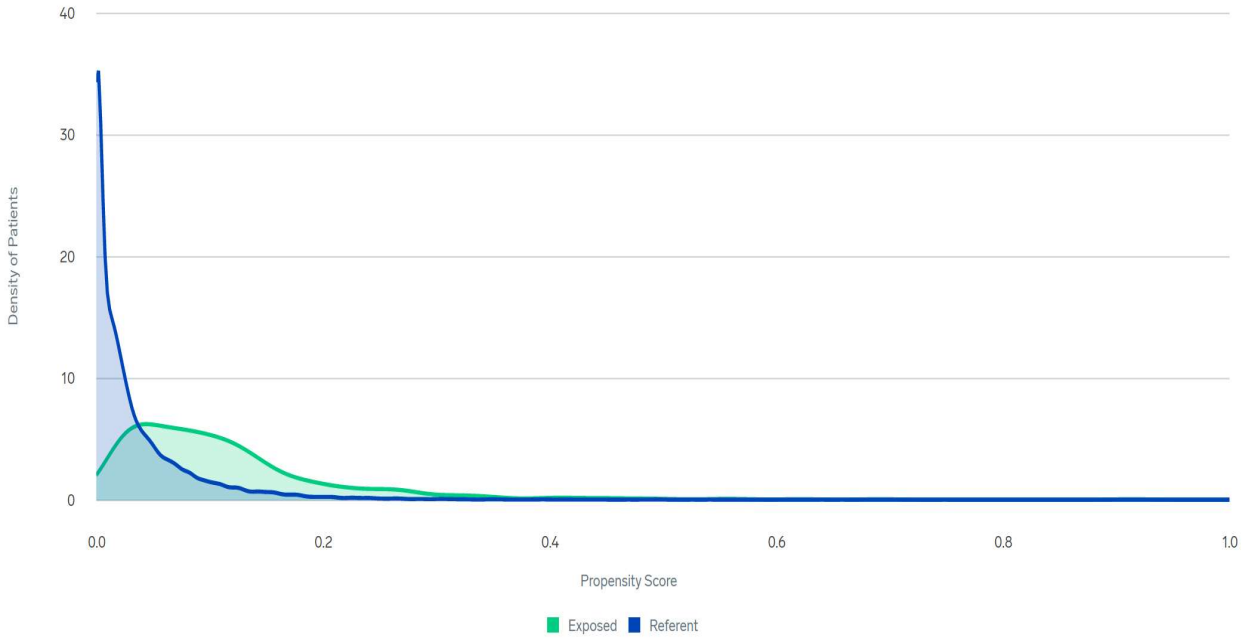
AFTER PS MATCHING



Appendix B: Propensity

Semaglutide vs Standard - Cohort AT 12-30w

BEFORE PS MATCHING



AFTER PS MATCHING