DRIVE Program: Diabetes Remote Intervention to improVe use of Evidence-based medications

Statistical Analysis Plan

November 16, 2023

Study Information

Title	**DRIVE** Program: **D**iabetes **R**emote **I**ntervention to impro**V**e use of **E**vidence-based medications
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Research question and objectives	● Create a remote diabetes management platform to improve adherence to new guidelines regarding use of glucose-lowering medications with cardiovascular and renal benefit for patients with type 2 diabetes and high cardiovascular and/or renal risk. ● Increase patient disease knowledge, activation, and engagement. ● Evaluate optimal timing of patient education within the program.

Research Question and Objectives

The overarching goal of the DRIVE Program is to partner with and support physicians to overcome the well-recognized therapeutic inertia that delays the adoption of new evidence-based therapy and prevents patients from achieving recommended care targets.

In this project, we will use a collaborative drug therapy management (CDTM) agreement to allow a pharmacist, in collaboration with a patient navigator, to initiate, discontinue, and titrate SGLT2i, GLP-1 RA, and other diabetes medications based on an algorithm developed by physicians.

Importantly, medication selection and recommendations in this program are based on guideline recommendation and standard of care. In this project, the patient will be provided with education and therapeutic recommendations and will then decide whether to start a new medication and which medication to start if there is equipoise between medications. Patients are not "assigned" to take a specific medication in any of the navigator-CDTM interventions, if there is equipoise.

Roughly 50% of patients enrolled into this quality improvement program will be allocated into an "education first" pathway, which will provide 4 weeks of digital, paper, and customized video resources to explain the medical rationale and anticipatory guidance regarding diabetes care and therapeutics with proven benefit prior to becoming eligible for medical therapy prescription. In addition to looking at uptake and adherence, we will be measuring baseline and end-of-study Patient Activation Measures for each participant. Patient Activation Measures have been shown to correlate with increased self-care behaviors, medication adherence, and diabetes monitoring (11).

Primary Aim

The primary objective of this study is to create a remote diabetes management platform that compared to baseline, will improve initiation and adherence to contemporary guidelines regarding the use of glucose-lowering medications with cardiovascular and renal benefit for patients with type 2 diabetes and high cardiovascular and/or renal risk.

Secondary Aim(s)

- Evaluate optimal timing of patient education within the program. (measured as prescriptions by randomization arm, prescriptions at 2 months, and patients on therapy at end of study)
- Increase patient disease knowledge, activation, and engagement (as measured with short-form Patient Activation Measure)

Exploratory Aim(s)

Weight and HbA1c

We will compare age, socioeconomic demographics (where available), baseline characteristics and medical history, HbA1c, and demonstrate that they are evenly distributed in the population and between groups. We will report subgroup-specific rates if there are significant differences (e.g., evidence of heterogeneity).

Data Sources

Data will be collected from the electronic health record (HER) and directly from patients. All data will be stored in an encrypted, secure database within the Mass General Brigham firewall and using HIPAA-compliant applications.

Study Sample Size

Primary Outcome: By design, no patients will be on SGLT2i or GLP-1 RA therapy at baseline. We are excluding patients who are on the drugs of interest at baseline, so our primary outcome is the proportion of prescription therapy provided at 6 months. Our null hypothesis is that with we would expect with our education only (control) arm to increase rate of prescription from 0% to 5% based on secular trends and from 0% to 20% increase in SGLT2i or GLP-1 RA therapy in our intervention group utilizing navigators. 100 patients per arm will allow a 25% dropout rate to maintain power > 80% to maintain an alpha level of 0.05. As we are comparing the timing of education in the A/B allocated groups, we expect that our sample size will provide ~80% power to detect an absolute rate of prescription difference of 15% between our immediate titration and education prior to titration groups (i.e., at 3 months)

Secondary Outcomes: With a mean HbA1c of 7.2% and a standard deviation of 1%, to obtain 80% power to detect a 0.5% difference in HbA1c, we would need to enroll 63 patients per arm (preliminary data.) To account for dropout, (expecting 25% dropout) we will calculate N1= n/(1-dropout rate) => 63/0.75 = 84 patients per arm.

Data Management

Mass General Brigham will create a data collection instance within the patient-management application. All data will be collected and stored within the Mass General Brigham firewall in a HIPAA-compliant, encrypted server, key variables data will be randomly sampled and verified for accuracy in 40 patients representing 20% of the study population. Data will be stored for at least 5 years after project completion.

Data Analysis

We will utilize SAS software, version 9.4 (SAS Institute) to conduct our statistical analysis.

There will be ongoing quality checks of the data. Before final analysis, the data will be queried for outliers and missing data. The primary analysis will not impute any missing data though sensitivity analysis may use imputation methods such as last observation carried forward (LOCF).

Definition of Analysis Sets

For the Full Analysis Set (FAS) Patients will be included all patients enrolled (intention-to-treat analysis.)

The Per protocol Set (PPS) will include patients that did not drop out or become unreachable and completed the entire quality improvement program.

Statistical Methods

For our primary outcome, the percent of patients on either an SGLT2i or GLP-1 RA from baseline to conclusion of the study at 6 months post-enrolment, we will perform a Chi-Square test to determine a difference in the terminal rates at the end of the study to determine treatment effects between groups.

We will develop a cumulative incidence curve displaying patients both prescribed and taking DRIVE medications for the duration of the program.

We will perform t-tests and Fisher's exact test for the baseline univariate analysis. As we will be utilizing A/B allocation there should be no bias or confounding at baseline, however if any significant differences are found, we will correct for these utilizing logistic regression. A/B allocation with 200 patients should cause any confounders to balance between the groups. We will also perform a longitudinal model for binary outcome at 6 months. For our co-secondary outcomes, the change in the HbA1c, and PAM from baseline to the end of the 6-month study, these will be analysed with a paired t-test and we will report a mean and standard deviation. A secondary analysis will be to conduct linear regression models with two variables (baseline HbA1c and baseline weight) to control for any confounders.

We will conduct our analysis via the intention-to-treat principle with two-sided type I error with an alpha of 0.05. For participants with missing outcome data, we will perform a sensitivity analysis with missing outcomes excluded or included as an event.

A priori sub-analyses will be performed based on zip code, baseline HbA1c, race, insurance status, and sex with a p-value threshold of 0.1 for these secondary analyses and we will account for multiple testing. A cox proportional hazards model will be performed to assess time-to-prescription between groups.

After the final data was reviewed, a series of subsequent hypotheses were identified for additional analysis. These analyses are, by definition, post hoc and, therefore, considered hypothesis-generating. A p-value of 0.05 will be considered significant without any correction for multiple comparisons.

Interim Analysis

N/A

Quality Control

Data will be collected from our EHR, the MGB Electronic Data Warehouse (EDW), and patients. Clinical laboratories within MGB system have laboratory certificates available upon request.