AstraZeneca

Statistical Analysis Plan

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ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus (ENGAGE-DM):

A 12-month study of the impact of combined shared-decision making and brief negotiated interviewing on disease control and medication adherence in patients with diabetes

ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus (ENGAGE-DM)

Study Statistician

ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus (ENGAGE-DM)

Global Product Statistician

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Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
HbA1c	Glycosylated hemoglobin
ICD-10	10th revision of the International Classification of Diseases
LSLV	Last Subject Last Visit
PDC	Proportion of Days Covered
T2DM	Type 2 Diabetes Mellitus

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1. STUDY DETAILS

1.1 Study objectives

The **primary objective** is to examine whether a two-stage process of shared decision-making and behavioral interviewing improves glycosylated hemoglobin (HbA1c) control and medication adherence among patients who have poorly-controlled diabetes.

The **secondary objective** is to develop prediction models and examine their ability to predict response to the study intervention based on baseline patient characteristics, such as sociodemographic, clinical, and medication use characteristics.

1.2 Study design

ENGAGE-DM (ENhancing outcomes through Goal Assessment and Generating Engagement in Diabetes Mellitus) is a pragmatic, prospective, intention-to-treat, randomized controlled trial designed to examine the impact of a novel intervention among patients with T2D that combines behavioral interviewing and shared decision-making delivered by pharmacists over the telephone compared with usual care. After the completion of the trial, we will examine whether a patient's response to the intervention could have been predicted based on their demographics, comorbidities or medication treatment-related factors.

This trial is being conducted among commercially-insured individuals whose medical and prescription benefits are administered by Horizon Blue Cross Blue Shield of New Jersey (Horizon). Horizon is the largest health insurer in New Jersey and administers plans for over 3.8 million beneficiaries.

Following the principles of pragmatic trial design, potentially eligible patients for inclusion in this study were those who: (1) were ≥18 years of age, (2) had filled a prescription for 1 or more oral hypoglycemic agents within the prior 12 months, and (3) had evidence of poor glycemic control (A1C ≥8%) within the previous 6 months, assessed using the most recent HbA1c lab values provided to Horizon Blue Cross Blue Shield. If patients had multiple HbA1c lab values, the latest value was evaluated. An HbA1c threshold of 8% was chosen based on the minimum threshold that nearly all patients should achieve based on guidelines from the American Diabetes Association (ADA); it is also a threshold for major quality measures for health plans. Patients were excluded if, prior to identification, they had fewer than 3 months of continuous enrolment in the health plan, had recently filled insulin (e.g., to exclude patients with type 1 diabetes), or had no available telephone contact information, which would preclude contact for enrolment and delivery of the intervention.

1.3 Number of subjects

In total, 1,400 subjects were randomized in a 1:1 ratio to the intervention or control group. Our study was designed to be sufficiently powered to detect small but clinically meaningful changes in the primary outcome of HbA1c change.

We considered the following assumptions in the power calculations. Assuming that 30% of study subjects in the intervention arm agree to participate in the intervention, we randomized 700 individuals

to each of the intervention and control groups in order to achieve 80% power to detect an average change in HbA1c of 0.5% between the intervention and control groups at an alpha threshold of 0.05 with a HbA1c standard deviation=1.9 (the most commonly cited value in the literature for HbA1c), accounting for 25% rate of loss-to-follow-up.[1,2] We used Proc Power in SAS 9.4 (Cary, NC) using a t-test and adjusted the sample size to account for the reach rate. Because patients may change insurance, in particular at the end of the calendar year, we accounted for a rate of non-differential loss-to-follow-up of 25% rate. There may also be patients who do not have follow-up HbA1cs, despite restricting to patients whose providers have at-risk contracts with Horizon Blue Cross Blue Shield. As described later in Section 3, we will use multiple imputation methods to account for patients with no follow-up HbA1c values. In addition, this proportion of patients who agree to participate in this intervention has been observed in prior studies that have used a similar approach.[25] Finally, the proposed difference of HbA1c of 0.5% is the level that clinical guidelines consider to be a clinically meaningful difference in glycemic control. This HbA1c difference has also been observed in prior work with clinical pharmacists.[8] Because the primary outcome is HbA1c change, we expect to see clinically meaningful differences in these levels within the 11 to 12-month follow-up period.[3,4]

For secondary outcomes, with this sample size, we will also have the power to detect at least a 4% absolute difference in adherence (i.e., mean PDC levels) between the intervention and control groups, assuming baseline rates of adherence of 50%. We used Proc Power in SAS 9.4 (Cary, NC) using a chi-square test and adjusted the sample size to account for the reach rate. These differences in adherence have been observed as meaningful in prior research, and the baseline rate of adherence is based on prior research in this field.[5-7] In addition, prescription claims will be captured on all patients included in the study by definition for inclusion, enabling the calculation of adherence in the follow-up period until loss of continuous eligibility. Therefore, there is no substantial lost-to-follow up expected for this outcome.

Finally, for the secondary objective (Aim 2), this sample size would also provide enough patients for the predictive modelling, given the relative non-rare nature of the study outcomes (glycemic control and medication adherence) and number of predictors considered per number of patients in the study.[8]

2. ANALYSIS SETS

2.1 Definition of analysis sets

Full Analysis Set (Intention to Treat population): The primary and secondary outcomes will be evaluated using intention-to-treat principles among all randomized patients. Within the intervention group, patients who choose to speak with a pharmacist may differ from those who do not, and therefore an intention-to-treat analysis in this randomized study ensures unbiased comparisons to the control group. Therefore, the analysis set for the primary and secondary objectives will be the intention-to-treat population of all patients who meet inclusion and exclusion criteria and are randomized to the trial.

As-treated/per-protocol Analysis Set: We will also explore an "as-treated' analysis that compares patients in the intervention group who received the pharmacist intervention with patients in the usual care group. For this analysis set, the subgroup of patients in the intervention group who agreed to participate in the intervention will be compared against the patients in the control group. This analysis set will not be used for any of the primary analyses, only secondary analyses.

2.2 Violations and deviations

We have not identified any important protocol deviations in this study to date. To our knowledge, no patients were erroneously randomized (in that they did not actually meet inclusion or exclusion criteria at the time of randomization). In other words, at the time the assignment was actually performed in Oct 2016 and Dec 2016, all patients were eligible for the study.

However, once the database lockout for follow-up outcomes is complete (late March 2018), Horizon will be sharing the full data, including prescription claims, medical claims, enrolment files, and laboratory values, to the [redacted] investigators for study analysis. Once these data are cleaned and the analytic dataset is generated, it is possible that a few patients may appear to have been erroneously randomized because there may have new lab values provided to Horizon that were not actually available to Horizon at the time the allocation was performed. In addition, because of the minor lag between pulling the data, evaluating eligibility in insurer claims data, and the subsequent randomization done by Horizon, it is possible that a small percentage of individuals may have terminated their medical or prescription drug benefits and could no longer be eligible.

Based on prior studies of insurance trials conducted in claims data, we anticipate that no more than 5% of patients may be subject to any protocol deviations related to insurance data lag or adjudication.[4,5,9] Moreover, we do not expect that there will be any differential deviations between the two study arms, so the study results should be unbiased. Regardless, patients who are found to have not met these enrolment criteria once the data is received will not be included in either of the Analysis Sets. Similarly, in the rare case that patients are found to have randomized multiple times or if there were any other unanticipated deviations, they will not be included in the Analysis Sets. We do not expect any of these potential deviations to affect the validity of the study results as they are not expected to be differential between the study arms.[9]

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary outcome (mean change in glycemic control):

The primary outcome of interest will be the pre- to post-intervention change in mean HbA1c levels to the end of the 12-month follow-up period. Follow-up will begin from the date of treatment group assignment. The data for this outcome will be based on laboratory information that Horizon Blue Cross Blue Shield of New Jersey receives from over 200 patient-centered medical homes and other population health programs used for quality improvement monitoring. This laboratory information will be used to measure the change in HbA1c levels at the end of follow-up. In specific, the HbA1c result recorded closest to the 12-month end of follow-up as provided in the laboratory data will be used for the primary analysis.

For subjects with missing outcome data, multiple imputation will be used to impute missing follow-up values to calculate the change in HbA1c levels.[10] Of note, all patients by definition for inclusion in the study will have baseline HbA1c values. This imputation approach is used to generate multiple results for missing values based on the underlying distribution of the available data. We will test the robustness of this approach with sensitivity analyses that use alternative methods of handling missing data, including complete case analysis.

This outcome will be analysed formally. We will also explore any potential differences in effectiveness by the pharmacist delivering the intervention.

3.2 Secondary outcome (proportion achieving glycemic control):

The secondary glycemic outcome will include the proportion of patients achieving optimal glycemic control. Optimal glycemic control will be defined as the proportion of patients who achieved an HbA1c result <8.0% in the 12-month follow-up period. This conservative threshold is based on the minimum threshold that nearly all patients should achieve based on guidelines from the American Diabetes Association (ADA) and quality measures used to assess the performance of health plans.[11,12] In specific, we will use the laboratory information provided to Horizon and will use the HbA1c result recorded closest to the 12-month end of follow-up for the primary analysis.

For subjects with missing outcome data, we will use multiple imputation to impute missing follow-up values to calculate the proportion of patients who achieved this threshold.

This outcome will be analysed formally.

3.3 Secondary outcome (two medication adherence outcomes):

Medication adherence will be measured using filling patterns in pharmacy claims data for medications that qualified a patient for inclusion in the study.[13] For each medication, we will create a drug supply diary linking all observed fills after initiation based on dispensing date and days' supply. Different drugs in the same chemically-related therapeutic class (e.g., sulfonylureas) will be considered to be interchangeable. We will allow for up to 180 days of carryover supply. From these supply diaries, we will calculate the proportion of days that patients had medications available to them, or the proportion of days covered (PDC), by dividing the number of days with medication available by the number of days during follow-up.[14] If a patient loses continuous eligibility during the year after the index date, the PDC will be calculated based on the number of days available. If a patient loses continuous eligibility during the year after the index date, they will be censored on that date, and the PDC will be calculated based on the number of days available. In this PDC measurement, if patients had at least one antidiabetic medication available, then they will be considered to be adherent for that day. This definition allows for outcome measurement even when patients switch (e.g., switch from metformin to a sulfonylurea) or intensify therapy (e.g., adding a second oral diabetes medication or injectable medication).

Using this PDC measure, we will observe *1) the mean PDC in each study arm* and 2) *the proportion of patients achieving optimal adherence* (defined by ≥0.80 PDC) as adherence outcomes in the follow-up period. In a sensitivity analysis of this outcome, medication adherence will be measured by calculating the PDC beginning from the first fill of a medication after assignment until the end of the 12-month follow-up. There will be no missing data for these outcomes, as previously described.

These outcomes will be analysed formally.

3.4 Secondary analyses:

Resource utilization:
As secondary analyses, we will also measure healthcare spending and healthcare resource utilization, including outpatient visits, emergency room visits, and hospitalizations, in the follow-up period in the medical and pharmacy claims data. Healthcare spending will be measured as total allowed amounts in

the 12 months after randomization or until they lose continuous enrolment in both the medical and pharmacy claims files. This spending will sum the insurer paid amounts, coinsurance, copayments, and deductibles paid by patients. Healthcare resource utilization will be measured in the medical claims data. In specific, we will measure the count of outpatient office visits to providers, the count of emergency room visits, and the number of times each patient was hospitalized as outcomes from their randomization date until 12 months after randomization or until they lose continuous enrolment. These outcomes will be analysed formally.

Medication adherence:
Other medication adherence measurements will also be assessed descriptively, including adherence to each individual anti-diabetic medication, the proportion of patients who were adherent (defined by ≥80% PDC), and gaps in medication availability. For these definitions, rates of switching, augmentation, discontinuation and other changes in prescription patterns will also be measured descriptively. Adherence to each diabetes medication will be measured using PDC, adjusting the denominator for new medication based on the number of days in the follow-up period that medication was used for. Persistence to medications will also be assessed, defined as a gap in supply of ≥60 days following exhaustion of the drug supply in the follow-up period. If insulin is used adjunctively or instead of oral therapy, persistence to insulin will also be measured. This approach to multiple medications has been used in other studies by our study group.[3,15] These are planned to be measured descriptively.

Uptake of intervention:
We will also descriptively examine the number of follow-up calls and the number of patients who choose each type of decision (e.g., treatment intensification or adherence/lifestyle improvement). This will be based on de-identified call data provided by [redacted] (the pharmacists delivering the intervention).

4. ANALYSIS METHODS

4.1 General principles

The primary objective is to examine whether a two-stage process of shared decision-making and behavioral interviewing improves glycosylated hemoglobin (HbA1c) control and medication adherence among patients who have poorly-controlled diabetes. This is a superiority trial.

The primary outcome is pre to post change in mean HbA1c level from baseline to the follow-up period. There is only one primary outcome, so there will be no multiple testing adjustments.

The primary and secondary outcomes will be evaluated using intention-to-treat principles among all assigned patients. Within the intervention group, patients who choose to speak with a pharmacist may differ from those who do not, and an intention-to-treat analysis in this randomized study ensures unbiased comparisons to the control group.

For all outcomes, statistical significance is defined based on $p<0.05$ level and using two-sided steps. For continuous data, we will present the results as n and mean (standard deviation). For binary data, we will present the data as n (%). We further describe the analysis of and tests used for each of the outcomes in Section 4.2.

The secondary objective is to develop prediction models and examine their ability to predict response to the study intervention based on baseline patient characteristics, such as sociodemographic, clinical, and medication use characteristics, as well as initial receptiveness to changing health behaviors. We will describe the analysis of this objective further in Section 4.2.

4.2 Analysis methods

4.2.1 Primary objective (Effectiveness of intervention):

Baseline characteristics:
We will measure key baseline characteristics in the 12-months prior to randomization in the pharmacy and medical claims data and enrolment files. These characteristics will include sociodemographic characteristics, such as age and sex, which will be measured in the enrolment files. We will also measure baseline clinical characteristics such as the presence of coronary artery disease, chronic obstructive pulmonary disease, asthma, hypertension, hyperlipidemia, congestive heart failure, depression, liver disease, chronic kidney disease, osteoporosis and prior macrovascular complications. These will be measured in medical claims files using ICD-10 codes. We will also measure the type of oral glucose-lowering agent used in the baseline period (e.g., medical class), average PDC at baseline, and whether or not the medication is branded. We will also measure patients' latest copayments for oral glucose-lowering agents in the baseline period. Finally, we will also measure baseline healthcare resource utilization variables as characteristics including the number of days hospitalized and the number of physician office visits.

We will report, in tabular format, the means and frequencies of baseline characteristics prior to assignment separately for patients in the intervention and control groups and compare these values using t-tests, chi-square tests, and their non-parametric analogues, as appropriate. We will provide absolute standardized differences between the two treatment groups.

Primary analyses:
Primary outcome (change in HbA1c): In the primary analysis, the primary outcome, mean change in glycemic control, will be compared using generalized estimating equations with an identity link function (as a continuous variable) and normally distributed errors within the imputed full analysis set, as described above. Data will be presented as the unadjusted absolute difference in the change in HbA1c between the groups along with 95% confidence intervals.

Secondary outcome (proportion achieving glycemic control)
1) *Proportion of patients achieving optimal glycemic control* (defined by HbA1c<8): This outcome will be compared using generalized estimating equations with a logit link and binary distributed errors. Data will be presented as the unadjusted odds ratio for optimal glycemic control between the groups along with 95% confidence intervals.

Secondary outcomes (medication adherence):
1) M*ean PDC in each study arm:* This outcome will be compared using generalized estimating equations with an identity link function and normally distributed errors. Data will be presented as the unadjusted absolute difference between the groups along with 95% confidence intervals.
2) *Proportion of patients achieving optimal adherence* (defined by ≥0.80 PDC): This outcome will be compared using generalized estimating equations with a logit link and binary distributed errors. Data will be presented as the unadjusted odds ratio for optimal adherence between the groups along with 95% confidence intervals.

Secondary analyses:
Healthcare resource utilization and spending: Secondary analyses of healthcare resource utilization will use a similar approach as the primary analysis among the full analysis set, except that we will use log link functions with Poisson errors to describe the count data. Health spending will also be evaluated with variances proportional to the mean (e.g., Poisson-like errors) using log-link functions in generalized estimating equations, which has been found to describe insurer healthcare spending data accurately based on prior research.[5] Data will be presented as the unadjusted odds ratio along with 95% confidence intervals.

Adjusted analyses: If there are differences in baseline characteristics between study groups that are believed to be confounders (defined by a standardized mean difference of >0.1), we will repeat all of our analyses for the primary and secondary outcomes after adjusting for these covariates in multivariable regression. We will present these as adjusted effect estimates along with 95% confidence intervals.

Interactions: We will also explore any potential differences in effectiveness by the specific pharmacist delivering the intervention by evaluating effect measure modification and using interaction terms within the main model for the primary outcome of change in HbA1c. We will present p-values for interactions.

Subgroups: Subgroup analyses of the primary outcome (change in HbA1c) will also be performed for key subgroups, according to age, sex, depression, and baseline medication adherence levels. These analyses will be performed separately among subgroups of the characteristics and compared between the treatment arms. Data will be presented as unadjusted absolute differences in the change in HbA1c along with 95% confidence intervals.

Sensitivity analyses:
For the glycemic control outcomes, we will also conduct a complete case analysis among patients with complete HbA1c follow-up data. We will also repeat our analyses with longitudinal modeling methods in generalized estimating equations that incorporate any additional HbA1c laboratory values in the 12-month follow-up period, for both the primary outcome of change in HbA1c and secondary outcome of the proportion achieving optimal control.

4.2.2 Secondary objective (Prediction modelling):

Overview
As a secondary aim, we will use predictive analytic approaches to examine whether the clinical outcomes could have been predicted based on patient factors, such as sociodemographic, clinical, medication use and receipt of the pharmacist-delivered telephonic intervention. The goal is also to identify patients who were most likely to respond to this type of intervention. In this aim, we will retrospectively examine whether these characteristics predict glucose control (e.g., HbA1c<8%) and medication adherence (e.g., PDC≥0.80). Specifically, we will evaluate prediction models with respect to their ability to discriminate and explain variation between patients who did and did not meet the glycemic and medication adherence targets during the follow-up period.

Model definitions:
To assess the ability to predict patients who will respond to the intervention, for each outcome (e.g., HbA1c<8% and PDC≥0.80), we will develop and estimate a series of logistic regression models for patients in both the treatment and control groups, incorporating different patient characteristics

(described in 4.2.1) as predictors. We will model these particular outcomes because these are considered to be clinically meaningful cut-points for achieving optimal control for diabetes and adherence, respectively, and will be meaningful measures for providers, policymakers, and payers alike. For these models, the outcome will be treatment response as defined by each outcome and will include different numbers of predictor variables, in a method similar to previous work.[16,17] As predictors in these models, we will incorporate patients' baseline demographic, clinical, and resource utilization characteristics.

Model estimation and validation:
For each outcome (e.g., HbA1c<8% and PDC≥0.80), we will first estimate a model that includes only demographic and clinical characteristics. We will then estimate additional models that include these predictors as well as baseline medication adherence. Receipt of the pharmacist intervention will be tested using an interaction term so the logistic regression will provide estimates on all patients and not just those receiving the intervention. We will also repeat the analyses among the subgroup of intervention patients who had at least 1 telephonic encounter with a pharmacist to examine which set of characteristics are most predictive of the response to the intervention. Model estimation will be repeated among relevant patient subgroups (e.g., gender, age) to see if there are any differences in predictive ability.

Models among each of the control and intervention groups will be predicted using both logistic regression and generalized boosting regression, a data mining technique that generates a prediction model through building many regression trees with the potential for many interactions among the predictors.[18] Through these many regression trees, the model can incorporate a number of non-linear associations between the predictors and the outcomes; this approach is considered to be one of the best prediction approaches. Alternative methods of clustering patients who are most likely to respond will also explored, including machine learning to develop models algorithmically, to partition patients into clusters that have a similar likelihood of experiencing the clinical outcomes.[19]

Model accuracy:
To compare the accuracy of the prediction models, we will compare discrimination, the ability of the model to distinguish between patients who do and do not experience the outcome, by the C-statistic. A C-statistic of 1.0 indicates perfect prediction and a value of 0.5 indicates no association.[8,20] Pseudo R-squares will be used to assess model performance by examining the degree of variation explained by the model, ranging from 0 (no variation explained) to 1.0 (all variation explained) [21]. As secondary analyses, we will also model the change in HbA1c as well as continuous PDC at the end of the follow-up period using linear regression and boosted linear regression, using R-squares to examine predictive ability. To avoid "over optimism" bias associated with evaluating prediction accuracy in the same data used for estimation, we will perform 10-fold cross-validation, which randomly partitions a sample of data into different partitions (leaving 10% of the data out each time) 10 times and averages the validation results over the 10 repetitions.[8]

5. INTERIM ANALYSES

N/A

6. CHANGES OF ANALYSIS FROM PROTOCOL

N/A

7. REFERENCES

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8. APPENDIX

N/A