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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

Sponsor:

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

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

Principal Investigator: [redacted]

Study site(s) and number of subjects planned

This prospective study will include 1,400 beneficiaries of Horizon Blue Cross Blue Shield of New Jersey (BCBSNJ). We plan to primarily include participants who receive care in a number of Patient-Centered Medical Homes (PCMHs) and other population health programs that collaborate with Horizon BCBSNJ. There are no investigational drugs being used in this study. The Privacy Board of Horizon Blue Cross Blue Shield of New Jersey has approved this study protocol.

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2016	N/A
Estimated date of last subject completed	Q2 2017	N/A

Study design

In this study of patients on at least one oral hypoglycemic therapy with poorly controlled disease, we will examine the effect of pharmacist-delivered patient engagement techniques combining shared-decision making and brief negotiated interviewing on disease control and medication adherence compared with usual care. Briefly, all patients allocated to the intervention will be mailed a patient decision aid to help prime them for encounters with pharmacists. After receiving the decision aid, these patients will be asked to provide informed consent to engage in at least 4 telephonic discussions with pharmacists about their diabetes treatment options, goals, and preferences, medication adherence, strategies for reducing adherence barriers, and the benefits of maintaining blood glucose control.

After the completion of the study, we will also use predictive analytics to examine whether treatment response could be predicted based on patient characteristics, such as sociodemographic, clinical, medication use, and other motivational characteristics. These predictive analytic techniques will include logistic regression, boosted regression, and machine learning approaches. The use of predictive analytics will provide policy-relevant

information about who is most likely to benefit from these patient engagement techniques in real-world practice.

Objectives

Primary Objective:	**Outcome Measures:**
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.	Glycosylated hemoglobin (HbA1c): - Primary outcome: Pre- to post-intervention change in mean HbA1c levels - Mean levels in each study arm in the follow-up period - Proportion of patients in each study arm achieving optimal HbA1c control in the follow-up period Medication adherence: - Continuous proportion of Days Covered (PDC) in each study arm in the follow-up period - Proportion of patients in each study arm achieving optimal adherence (PDC ≥0.80) in the follow-up period

Secondary Objective:	**Outcome Measure :**
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.	Predictive statistics: - Cross-validated C-statistics (discriminative ability of the model) - Cross-validated R-squares (explained variation in treatment response)

Safety Objective:	**Outcome Measure:**
N/A	N/A

Target subject population

We will examine commercially-insured patients from Horizon BCBSNJ who are ≥18 years of age, are using at least one oral hypoglycemic agent, are not currently on insulin, and whose HbA1c values indicate poor disease control (≥8%). Patients may be on multiple medications, including non-insulin injectables.

Duration of treatment

700 patients will be identified for the intervention and then followed for 12 months. During follow-up, the patients in the intervention group will be invited to receive repeated 'booster' interactions with pharmacists using the two patient engagement techniques to discuss their diabetes control, goals and preferences. Seven-hundred patients will also be identified for a control group and followed for the same duration of time.

Investigational product, dosage and mode of administration

N/A – we are examining the effect of a quality improvement intervention on diabetes outcomes and medication adherence. There are no investigational pharmaceutical products being tested in this study.

Statistical methods

The primary outcome of interest will be the pre- to post-intervention change in mean HbA1c levels from identification to the end of follow-up. Horizon BCBSNJ receives laboratory information from over 200 patient-centered medical homes and other population health programs. This laboratory information will be used to measure the change in HbA1c levels. We will use generalized estimating equations to compare the changes.

Secondary outcomes will include both glycemic outcomes and medication adherence outcomes. The secondary glycemic outcomes will include mean HbA1c levels and the proportion of patients achieving optimal glycemic control, defined as the proportion of patients who achieved a HbA1c <8.0%. Patients' adherence to their diabetes medications will be measured by pharmacy claims and their filling patterns. Adherence will be assessed using the proportion of days covered (PDC), or the proportion of days that patients had medication available to them during follow-up. We will also measure and examine other adherence and persistence measures as secondary outcomes, including mean PDC in each study arm, the proportion of patients achieving optimal adherence (defined by ≥80% PDC), and gaps in medication availability. Dichotomous outcomes will compared using logistic regression, and continuous outcomes will be assessed using linear regression.

After study completion, we will use predictive analytics to examine whether the outcomes could have been predicted based on patient factors, such as sociodemographic, clinical, medication use and adherence, other self-reported motivational characteristics, and receipt of the pharmacist-delivered telephonic intervention. These predictive ability of these models will be assessed using model discrimination and performance measures, using logistic regression, boosted regression and machine learning approaches.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IP	Investigational Product
IVRS	Interactive Voice Response System
LSLV	Last Subject Last Visit
PDC	Proportion of Days Covered
SAE	Serious adverse event
T2DM	Type 2 Diabetes Mellitus

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Both developed and developing countries face a growing epidemic of type 2 diabetes (T2DM). Although medications can effectively reduce high blood glucose levels, poor disease control is common, leading to preventable complications such as stroke, heart disease, and kidney failure. In the United States alone, diabetes-related health expenditures exceeded $174 billion in 2007, with $58 billion spent on preventable complications.[1]

T2DM is a progressive disease and treatment of T2DM comprises a combination of lifestyle changes and drug therapy. Treatment with medications such as oral antidiabetic drugs (OADs) are the mainstay of therapy for many T2DM patients, but many do not achieve the optimal reductions in weight, blood pressure or glycated hemoglobin (HbA1c), and might benefit from additional therapy. However, among patients with poorly controlled T2DM, it is often not clear whether the problem is attributable to the healthcare provider's failure to appropriately intensify therapy, the patient's non-adherence to prescribed medications, the patient's unwillingness to accept new treatments or a combination of these factors.[2,3] There is growing evidence supporting several different patient-targeted interventions that could be employed in this exceptionally common situation.

Shared decision-making (SDM) is a patient-centered approach to improve the quality of care of patients with diabetes and other chronic conditions.[4] SDM describes the collaborative process where treatment decisions are made in a two-way exchange of information that integrates both the current medical evidence and the patient's needs and preferences, and could be used to facilitate treatment choices that is in keeping with a patient's own goals.[5-7] A 2014 Cochrane review found that shared decision-making, supported by decision aids, led to: a) improved knowledge of options; b) more accurate expectations of benefits and harms; c) choices more consistent with informed values; and d) greater participation in and improvement of decision making.[8]

While shared decision-making is often employed at a single time point in time when a discrete decision about treatments is made, the management of a chronic disease, such as T2DM, frequently requires ongoing follow-up and patient engagement. By contrast, behavioral interviewing techniques, such as motivational interviewing, are typically delivered longitudinally and repeatedly, but are not necessarily designed to help patients make decisions about how to improve their own care. For example, Brief Negotiated Interviewing (BNI), incorporates an active listening model of counseling to facilitate patients' evaluation of their health risks and treatment options.[9-12] This type of interviewing technique has motivational interviewing as its theoretical foundation and has shown promising results in improving adherence in other settings.[13-15]

Multi-component pharmacist-delivered interventions, particularly those rooted in patient engagement, have been shown to be some of the most effective interventions available to improve adherence to chronic disease medications.[16] In this spirit, even though SDM and BNI are complementary patient engagement techniques, no data are available on the effectiveness

of combining these 2 intervention approaches – especially in the management of T2DM. In addition, few studies have used telephonic methods to deliver either of these behavioral techniques. Evaluating these techniques in tandem in a telephonic manner that is scalable, cost-effective (especially compared with in-person delivery), and innovative will provide invaluable information to healthcare providers, decision-makers and insurers to improve diabetes management.

After the study is completed, the second phase of the project will use predictive analytics to examine whether patients' response could have been predicted based on patient characteristics, such as sociodemographic, clinical, medication adherence characteristics, and initial receptiveness to changing health behaviors. These findings will provide valuable information about which patients will benefit from the intervention moving forward. Once disseminated, the results of this study will provide multiple benefits to stakeholders, not only about the effectiveness of these patient engage techniques, but also about how to effectively target patients in real-world settings.

1.2 Rationale for study design, doses and control groups

Overall strategic purpose of CSP Section 1.2: To confirm appropriateness of study design to fully address study objectives, so that credibility of eventual clinical interpretation of the study data and conclusions will be enhanced.	
Physician representative	Has satisfactory medical and scientific justification been provided for key design decisions (including study duration, blinding, choice of comparator, choice of dose, frequency of dosing and time of day, route of administration) and for any lack of concordance with standard research practices or medical/statistical/regulatory guidelines?
Biostatistics representative	Has satisfactory justification been provided for key statistical design decisions (including study duration, blinding, choice of comparator, choice of dose, frequency of dosing and time of day, route of administration) and for any lack of concordance with standard research practices or medical/statistical/regulatory guidelines?
Regulatory representative	Have current regulatory guidelines and any outstanding Health Authority concerns been addressed? Does this section highlight and adequately address any potential limitations with study design (including study duration, blinding, choice of comparator, choice of dose, frequency of dosing and time of day, route of administration) that could be questioned by a Health Authority Reviewer?

Overall rationale and study population:

In this study of patients using at least one oral hypoglycemic therapy with poorly controlled disease, we will examine the impact of combining a shared decision making and behavioral interviewing intervention delivered telephonically by pharmacists compared with usual care. After study completion, as a secondary aim, we will also use advanced predictive analytics to

examine whether patient response could have been predicted based on patient characteristics, such as sociodemographic, clinical, medication use, and other motivational characteristics. This study and the use of predictive analytics to identify patients who most benefited from the intervention will provide policy-relevant information not only to Horizon BCBSNJ but also to other generalized audiences about who is most likely to benefit from these patient engagement techniques in real-world practice and target patients accordingly.

Seven-hundred patients who meet eligibility criteria will be allocated to the intervention group. These eligibility criteria are described in further detail in Section 3.

The intervention will be delivered by trained and licensed pharmacists from [redacted] a drug benefit management company that provides pharmacist-delivered telephonic disease management services. [redacted] has provided patient care services for other patient populations to a number of large insurers, including Horizon BCBSNJ.

The intervention is described in detail below.

Intervention: Shared decision-making/Brief negotiated interviewing

Eligible patients will first be sent an invitation letter. This letter will include a decision aid and pillbox that will prime them for telephonic encounters with pharmacists and will be used to enhance interventional efforts. This decision aid will be developed using principles of decision aid design and be based upon other decision aids that have been previously validated.[7,8,17,18] An online format for the decision aid will also be made available for patient convenience. Prior to study launch, the study team will solicit direct patient feedback on the decision aid and patient-oriented materials from a cohort of patient volunteers. The study team has established a relationship with local providers who lead regular diabetic support groups and has received their commitment to participate and solicit direct feedback. This patient feedback will be used to refine both the shared decision-making tool and other patient materials in accordance with guidelines on conducting shared-decision making in practice.[8,17]

To engage patients after the initial mailing and connect them with pharmacists more quickly and directly, an Interactive Voice Response System (IVRS) may also be used. One advantage of an IVRS is that it would provide a triage format for patients to contact the pharmacists directly after receiving the initial mailing. IVRS is frequently used in clinical practices and Horizon BCBSNJ to help manage their patients.

After the initial mailings, the pharmacists will attempt to reach each patient in the intervention group at least 4 times for the initial conversation. Each patient will be asked to participate in the intervention and provide verbal informed consent. After agreeing to participate by providing consent, the first telephonic encounter with the clinical pharmacist will consist of a 2-stage process of identifying patients' motivations and driving a consensus of decision choices. For these encounters, the [redacted] pharmacists will use a semi-structured call guide developed by the study team for both the initial intervention and follow-up 'booster' phone calls. These telephonic encounters will include discussions about diabetes treatment options, goals and preferences, medication

adherence, strategies for reducing barriers to adherence, implementing lifestyle modifications and the benefits of maintaining blood glucose control. In these consultations, both discrete decision support and ongoing motivational support will be provided to encourage medication adherence. If patients do not provide consent, they will not be contacted further.

In brief, the telephonic discussions with pharmacists will follow a semi-structured call guide that flows through the following phases (as part of the 2-stage process):

(a) confirm treatment regimens,
(b) discuss treatment goals and preferences,
(c) engage the patient in sharing potential medication non-adherence issues or lifestyle factors that may be contributing to poor control,
(d) discuss potential barriers and willingness/readiness to modify behaviors, and
(e) engage the patient in identifying and agreeing upon a possible shared plan of behavioral strategies to improve glucose control and potential treatment modifications.

The two stages of the call guide are summarized, as follows:

- Stage 1 Shared-Decision Making: The first stage of the intervention encounter consists of the shared decision-making process whereby discussions of issues and barriers to glucose control will be identified and discussed.
    - These discussions will occur in an open-ended manner, which will allow the patients to elaborate and problem solve as well as illuminate underlying beliefs and concerns that may affect glucose control.
    - The previously-mailed decision aid developed for telephonic use will be employed to aid in this encounter, which will to help the patient understand and reconcile the relative personal risks and benefits of medication adherence and treatment intensification to improve their disease control.
    - Ultimately, the goal of this first stage of the shared-decision engagement making process is patient involvement in the conversation and their care. The shared decisions may involve intensification of therapies for patients who are already adherent to their current regimen (as determined by patient self-report) or changing their medication adherence behaviors.

- Stage 2: Once coming to a shared decision between the pharmacist and patient about how to improve the patient's diabetes control, the second stage may involve a behavioral interviewing engagement technique if the shared decision involves adherence improvement as a goal.
    - This model incorporates an active listening model of counseling, identifying patients' readiness for change and level of behavior change using the Brief Negotiated Interview (BNI). This type of interviewing is built upon Prochaska's transtheoretical model of behavioral change, which posits that individuals move through a series of stages as they change behavior and identify interventions that are based on the individual's readiness for change.[19,20]

- The BNI employs some features of motivational interviewing but through a short structured interview that incorporates brief feedback and advice with motivational enhancement techniques.
- The BNI proceeds through the following four main steps: (1) raising support; (2) providing feedback; (3) enhancing motivation through assessing readiness and developing discrepancy between behavior and goals; (4) negotiating and advising.
- To develop the structured BNI tool within the call guide for this intervention, there are established algorithms that will be used.
- The goal of this stage is to motivate patients to change behaviors.

At the end of each conversation with the clinical pharmacist, a shared treatment plan will be identified, which will be modified upon each of the three subsequent encounters between the pharmacist and the patient. The barriers that will be addressed within the shared plan may include medication non-adherence but potentially also lifestyle modifications or issues with treatments, such as weight changes, low blood sugar, other side effect considerations, daily routines, any daily monitoring, and cost barriers. The barriers and proposed plan for each patient will be communicated from the pharmacist to the patient's provider, either via letters, faxes, and phone calls, depending on urgency. Ultimately any therapeutic decision (e.g. to change or intensify treatment) will be performed by the patient's own treating physician. For patients who decide through the course of this intervention to adhere to their currently prescribed treatment, they are following treatment recommendations already set forth by their providers.

These pharmacist-delivered phone calls will occur a minimum of 4 times during the follow-up period. The follow-up "booster" phone calls will repeat some of these themes and continue to engage the patient in discussions surrounding these topics.

Primary and secondary outcome measures

The primary outcome of interest will be the pre- to post-intervention change in mean HbA1c levels in each group. Horizon BCBSNJ receives laboratory information from over 200 patient-centered medical homes and other population health programs. This laboratory information will be used to measure the change in HbA1c levels at the end of follow-up. We will use generalized estimating equations to compare changes.

Secondary outcomes of interest include both glycemic outcomes and medication adherence outcomes. The secondary glycemic outcomes will include mean HbA1c levels at the end of follow-up and the proportion of patients achieving optimal glycemic control, defined as the proportion of patients who achieved a HbA1c <8.0%. Patients' adherence to their diabetes medications will also be measured by pharmacy claims and their filling patterns. Adherence will be assessed using the proportion of days covered (PDC) measure, or the proportion of days that patients had medication available to them during follow-up. Using this PDC measure, we will observe the mean PDC in each study arm and the proportion of patients achieving optimal adherence (defined by ≥0.80 PDC) as adherence outcomes in the follow-up period. Other persistence measures including gaps in medication availability will also be

descriptively measured. More detail on the measurement is provided in Section 8.1. Dichotomous outcomes will be compared using logistic regression, and continuous outcomes will be assessed using linear regression.

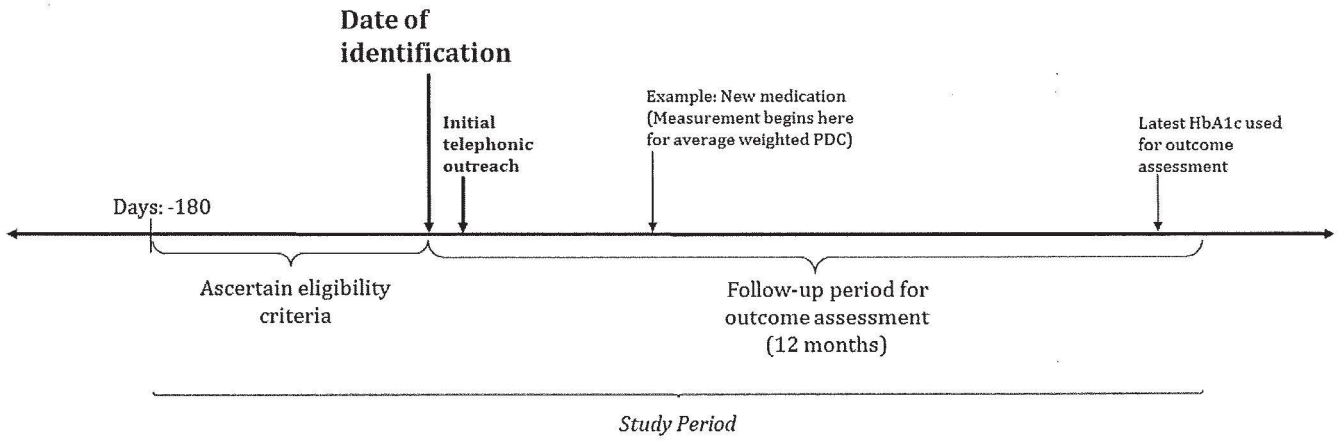
Study duration

700 intervention patients will be identified and then followed for 12 months.

After the completion of the study and database lock, we will use predictive analytics to examine whether the glucose control and medication adherence outcomes could have been predicted based on patient factors, such as sociodemographic, clinical, medication use and adherence, other self-reported motivational characteristics, and receipt of the pharmacist-delivered telephonic intervention. In brief, these predictive ability of these models will be assessed using model discrimination and performance measures, including logistic regression, boosted regression and machine learning approaches.[21-23]

A schematic of the study design and duration are shown in Figure 1 below.

Figure 1. Schematic of the study design and patient identification and follow-up periods



1.3 Benefit/risk and ethical assessment

Overall strategic purpose of CSP Section 1.3: To ensure the benefits and risks of the study are complete, accurate and consistent with the most recent evaluation of product benefit/risk, and that the study is ethically defensible.	
Physician representative	Through consultation with the Global Safety Physician, is the stated benefit/risk complete, accurate and consistent with the most recent evaluation of the product's benefit/risk? Is the study defensible from an ethical standpoint?

We have received Horizon Blue Cross Blue Shield Privacy Board approval to conduct this study including [redacted] use of a HIPAA limited dataset to conduct analysis on all identified intervention and control patients. In addition, we will seek [redacted] institutional review board approval for this strategy after study protocol approval by AstraZeneca. We have previously received approval for other studies using a similar study design and approach.

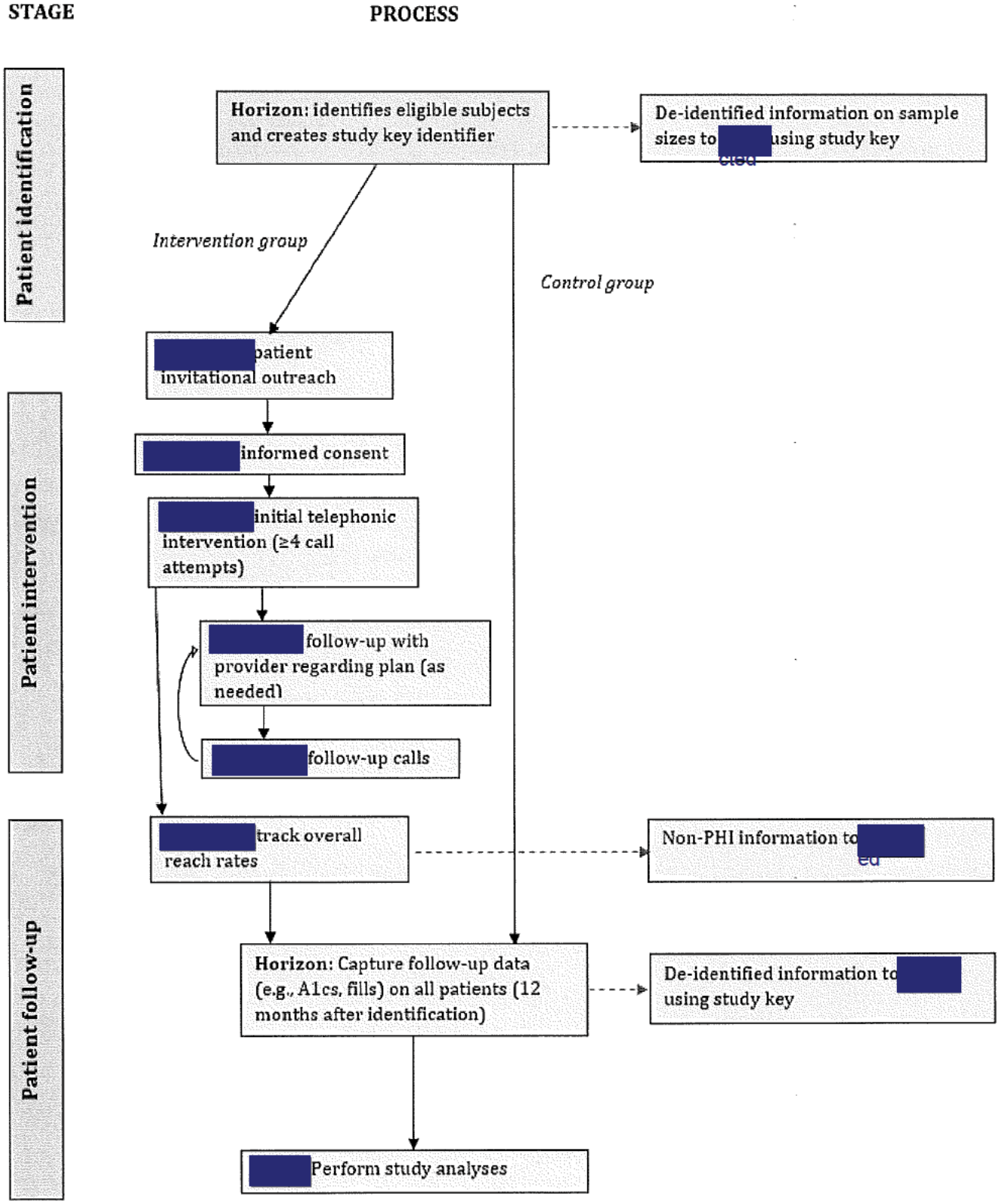
The risks to participating in this study are no more than minimal. First, no unapproved investigational products are being studied. Secondly, the risk to patients is no more than minimal, because healthcare data collected for the study were generated as part of routine care, including clinical diagnoses of diabetes as well as relevant laboratory results and medication prescription data. In addition, all treatment decisions will ultimately be made and overseen by the patient's provider.

Therefore, the primary risk to patients will be privacy of health information. To mitigate this risk, only the minimum amount of data necessary will be shared, and the key between the identifiers and the medical record number will remain at Horizon in a password-protected file. The [redacted] investigators will only have access to a HIPAA-limited dataset that includes dates and ages but no other identifying information. Limited information required for clinical care, similar to other interventions already with Horizon, will be shared with [redacted] and only a limited set of individuals directly caring for the patients will have access and access this information at any given time. In addition, all team members at both [redacted] and [redacted] have received appropriate and extensive training in data privacy.

1.4 Study Design

The overall study design and flowchart for ENGAGE-DM is shown in Figure 2.

Figure 2 ENGAGE-DM Study Flowchart



2. STUDY OBJECTIVES

Overall strategic purpose of CSP Section 2: To ensure the objectives are aligned with the purpose of the study, so that the study will generate the right type of evidence needed to fully support its purpose in the clinical programme.	
Physician representative	From a medical and scientific point of view, are the study objectives clearly written and strictly focused on what questions the study should provide answers to in order to support the tollgate decision, proposed CDS and/or TPP/TPCs?
Biostatistics representative	From a statistical point of view, are the study objectives clearly written and strictly focused on what questions the study should provide answers to in order to support the tollgate decision, proposed CDS and/or TPP/TPCs?
Regulatory representative	Assuming favourable study outcomes, will the study objectives support worldwide Health Authority approval of the proposed indication and recommendations for use contained in the proposed CDS?

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
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.	Glycosylated hemoglobin (HbA1c): - Primary outcome: Pre- to post-intervention change in mean HbA1c levels - Mean levels in each study arm in the follow-up period - Proportion of patients in each study arm achieving optimal HbA1c control in the follow-up period Medication adherence: - Continuous proportion of Days Covered (PDC) in each study arm in the follow-up period - Proportion of patients in each study arm achieving optimal adherence (PDC $\geq$0.80) in the follow-up period

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
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	Predictive statistics: - Cross-validated C-statistics (discriminative ability of the model) - Cross-validated R-squares (explained variation in treatment response)

2.3 Safety objectives

Safety Objective:	Outcome Measure :
N/A	N/A

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure :
N/A	N/A

3. SUBJECT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Overall strategic purpose of CSP Section 3: To define, and confirm appropriateness of, the study population, so that the proposed CDS will be fully supported by data obtained from the intended target population (including all relevant subgroups).	
Physician representative	From a medical point of view, do the proposed entry criteria accurately define the characteristics of the intended target population – noting any co-morbidities – and do they take into account the known safety profiles and restrictions of the investigational and comparator drugs? Is the study population too refined because of unduly excluding or screening out too many subjects from the study? Has satisfactory justification been provided for any discrepancies between the study population and the intended target population – noting possible consequences for the proposed CDS?

Overall strategic purpose of CSP Section 3: To define, and confirm appropriateness of, the study population, so that the proposed CDS will be fully supported by data obtained from the intended target population (including all relevant subgroups).	
Biostatistics representative	From a statistical point of view, do the proposed entry criteria accurately define the characteristics of the intended target population – noting any co-morbidities – and do they take into account the known safety profiles and restrictions of the investigational and comparator drugs? Is the study population too refined because of unduly excluding or screening out too many subjects from the study? Has satisfactory justification been provided for any discrepancies between the study population and the intended target population – noting possible consequences for the proposed CDS?
Regulatory representative	Is the study population representative of the intended target population, taking into account restrictions required in terms of available safety data (e.g., use in women of childbearing potential), and if not what could be the possible consequences for the proposed CDS?

Each subject will meet all of the inclusion and exclusion criteria for this study. Informed consent will be obtained from patients allocated to the intervention group prior to participating in the intervention. Horizon BCBSNJ currently has no direct outreach to patients in this commercially-insured population, so there should be no contamination for this study.

Horizon has an analytics request database in house where they describe what the data request is and what fields of information they may need for the pull. An analyst is then assigned to the request and pulls the data. To identify study patients, Horizon analytics will first apply the refined inclusion and exclusion criteria to existing administrative claims data.

We have received Horizon Privacy Board approval for the design and approach in this study. In addition, we have previously received IRB approval at [redacted] for other studies using a similar design and approach.[24,25]

3.1 Inclusion criteria

The following inclusion criteria will be used to refine the study population to ensure appropriate patients are included, while also maximizing generalizability of the study (Table 1). First, commercially-insured beneficiaries will be chosen because Horizon BCBSNJ currently does not have any direct outreach efforts to patients in this population. Limiting to patients who have Horizon BCBSNJ medical/prescription drug benefits ensures complete capture of information. We plan to primarily include participants who receive care in approximately two hundred Patient-Centered Medical Homes (PCMHs) and other population health management programs that collaborate with Horizon BCBSNJ but also include other members to enhance generalizability of the study population. Given the nature of the intervention and the validity of medication adherence measures, we will include patients in the

study who are using at least one oral hypoglycemic medication (Table 2). A HbA1c of ≥8% will be used to identify study patients, because multiple clinical guidelines concur that HbA1c levels this high indicate poor diabetes control. Lastly, due to the nature of the telephonic intervention, we will only include patients in the study who have provided non-missing phone numbers to Horizon; however, initial feasibility estimates indicate that this is most of their patients (85%).

Table 1. Patient inclusion criteria

Criterion	Operationalization
Commercially-insured beneficiaries	Horizon BCBSNJ beneficiaries with PCP
Aged ≥18 years	Based on age on index date (the date of identification)
Receive all medical/prescription drug benefits through Horizon	Based on having data available on the index date (the date of identification)
On ≥1 one oral hypoglycemic agent	Filled ≥1 oral hypoglycemic agent within the 365 days prior the index date (the date of identification) in pharmacy claims
Latest HbA1c measurement ≥ 8% (within previous 6 months)	Have an HbA1c ≥8% within the 180 days prior to the index date (the date of identification) in laboratory claims
Provided phone number to Horizon	Based on Horizon BCBSNJ enrollment data

Table 2. List of hypoglycemic agents for inclusion

Sulfonylureas	Meglitinides	Biguanides	Thiazolidine-diones	Alpha-glucosidase inhibitors	SGLT-2s	DPP-4 Inhibitors	GLP-1 RA
Chlorpropamide	Repaglinide	Metformin	Rosiglitazone	Acarbose	Canagliflozin	Sitagliptin	Exenatide
Tolbutamide	Nateglinide		Pioglitazone	Miglitol	Dapagliflozin	Saxagliptin	Liraglutide
Tolazamide			Troglitazone		Empagliflozin	Linagliptin	Albiglutide
Gliclazide			Tolazamide			Alogliptin	Dulaglutide
Glipizide							
Glyburide							
Glibencalamide							
Glimepiride							

Note: GLP1 medications will also be measured, but patients will have to be on at least one other oral agent. Fixed-dose combination products of these agents will also be included.

3.2 Exclusion criteria

A limited set of exclusion criteria will be used to identify eligible study patients to mimic the real-world nature of the study (Table 3). Because oral anti-insulin hypoglycemic agents are the primary medications of interest in this study, we will exclude patients who at the time of initial identification are using any insulin products. In specific, the management, measurement of medication adherence and use of patient engagement techniques in patients would differ if they are already using any human insulin or insulin analog.

Table 3. Patient exclusion criterion

Criterion	Operationalization
Currently using any insulin (listed below)	Insulin fill in previous 3 months in pharmacy claims data

List of insulin products for exclusion (any of the following – based on generic name)

- Rapid-acting: Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra)
- Short-acting: Regular (Humulin, Novolin, Velosulin)
- Intermediate-acting: NPH
- Long-acting: Glargine (Lantus), Detemir (Levemir)
- Mixes (Humulin, Novolin, Novolog, Humalog)

3.3 Subject enrollment

Patients will be identified by Horizon Analytics for the study. Seven hundred patients will be allocated to be eligible to receive the intervention. Patients allocated to the intervention group will be contacted by phone by [redacted] pharmacists and will be asked to provide informed consent to participate in the intervention. Verbal consent will be documented by the clinical pharmacist in [redacted] medical record. In addition, all calls will be recorded and available for auditing should re-confirmation of verbal consent be required. Seven hundred patients will also be identified by Horizon Analytics as a control group for analyses purposes only; these patients will not be contacted.

3.4 Criteria for withdrawal

Patients will not formally withdraw from the study unless they disenroll from a Horizon BCBSNJ plan, but their data will be collected until the loss of continuous enrollment, as was determined by the Horizon Privacy Board. In addition, patients identified for the intervention group will always have the option to withdraw their consent to participate in the intervention, and the pharmacists will then no longer try to make contact with these patients. These strategies have been used in previous studies.[26-29]

3.4.1 Withdrawal of the informed consent

The intervention itself involves helping patients set health-related goals and ultimately any therapeutic decision (e.g. to change or intensify treatment) will be performed by the patient's own treating physician. Patients can choose to no longer participate in speaking with the clinical pharmacists and withdraw their informed consent to participate in the study at any time.

3.5 Discontinuation of the study

Patients in the intervention arm who choose to not engage with the pharmacists or choose to later not engage with the pharmacists during follow-up will not be further contacted.

4. STUDY PLAN AND TIMING OF PROCEDURES

There are no formal visits in this study or any clinical procedures that will be conducted outside of routine care. We will not be requiring patients to seek care at any specified intervals to obtain study data to mimic real-world clinical practice.

The study plan and timing of the study interventions are shown in Table 4 below.

Table 4. Timing of study interventions

Study Arm	Initial mailing	Initial call	Follow-up call (#1)	Follow-up call (#2)	Follow-up call (#3)
Intervention group	Invitation letter	Consent + Introduction + SDM + BNI	Booster: SDM + BNI	Booster: SDM + BNI	Booster: SDM + BNI

4.1 Enrollment/screening period

To enhance the secondary predictive analytics aim of the study, [redacted] will capture some additional baseline information on patients assigned to the intervention arm during the initial call after obtaining consent. These patients will be asked to respond to a few survey questions. These additional items are anticipated to include a limited set of items on self-reported medication adherence, such as the 1-item Morisky adherence question[30,31], readiness to change[19], patient engagement, the Consumer Health Activation Index (CHAI), a marker for patient activation, and information about any baseline depression, including the Patient Health Questionnaire-2 (PHQ-2)[32]. Administered towards the beginning of the initial call, these questions will be built into the semi-structured call guide used by the pharmacists. The answers to these questions will not only help provide the pharmacists with additional information that is relevant to the two patient engagement techniques (and could be captured within these conversations in a less structured or validated manner), but will also be tested in the secondary predictive modelling study to identify the types of patients who will benefit from this intervention.

4.2 Treatment period

Patients will be followed from the identification until the end of the study. Patients in the intervention group will be contacted within their first month after identification, initially by mailed communication and then via the telephonic intervention. Follow-up "booster" telephonic phone calls by clinical pharmacists will be used at least 3 more times to support the intervention.

4.3 Follow-up period

As previously described, the follow up period will last for 12 months.

5. STUDY ASSESSMENTS

5.1 Efficacy assessments

The primary outcome of interest will be the pre- to post-intervention change in mean HbA1c levels to the end of follow-up. Horizon BCBSNJ receives laboratory information from over 200 patient-centered medical homes and other population health programs. This laboratory information will be used to measure the change in HbA1c levels at the end of follow-up. We will use generalized estimating equations to compare the changes between the two groups.

Secondary outcomes of interest include both glycemic outcomes and medication adherence outcomes. The secondary glycemic outcomes will include mean HbA1c levels at the end of follow-up and the proportion of patients achieving optimal glycemic control, defined as the proportion of patients who achieved a HbA1c <8.0%. Patients' adherence to their diabetes medications will also be measured by pharmacy claims and their filling patterns. Adherence will be assessed using the proportion of days covered (PDC) measure, or the proportion of days that patients had medication available to them during follow-up. Using this PDC measure, we will observe the mean PDC in each study arm and the proportion of patients achieving optimal adherence (defined by ≥0.80 PDC) as adherence outcomes in the follow-up period. Other persistence measures including and gaps in medication availability will also be descriptively measured. More detail on the measurement is provided in Section 8.1. Dichotomous outcomes will compared using logistic regression, and continuous outcomes will be assessed using linear regression.

5.2 Safety assessments

N/A

5.3 Other assessments

N/A

5.4 Pharmacokinetics

N/A

5.5 Pharmacodynamics

N/A

5.6 Biomarker analysis

N/A

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

There are no investigational products being examined in this study. If the clinical pharmacists become aware of any adverse event in a patient with an AstraZeneca product, they will report

any adverse event to AstraZeneca, refer to section 6.4. In addition, the clinical pharmacist is aware of any adverse event that are associated with manufacturers other than AstraZeneca, they will be encouraged to report them according to local requirements (health authority and/or manufacturer) through the spontaneous adverse event reporting system (Website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm). For serious adverse events (SAE), please refer to FDA website: http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm. We may request the study subjects/health care providers who report the adverse events (AEs) to disclose that the subject is involved in an observational study in which no study medications are administered.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from time of signature of informed consent throughout the completion of the study.

As previously described, any adverse events from the medications will be handled during the course of regular clinical care because there are no investigational products being studied. If the clinical pharmacists identify any adverse event with an AstraZeneca product they will need to report it to AZ as indicated in Section 6.4.

6.4 Reporting of adverse events and serious adverse events

If the clinical pharmacist becomes aware of an AE or an SAE with an AZ product they need to send the SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: [redacted] or send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox [redacted] (email is preferred method).

6.4.1 Reporting timelines

When informed by the clinical pharmacist that a SAE has occurred with an AZ product, the AZ representative (e.g. Patient Safety personnel at Marketing Company) will work with the clinical pharmacist to compile all necessary information and ensures that the AZ Patient Safety Data Entry Site receives a report within one calendar day of initial receipt for all fatal and life-threatening cases and within five calendar days of initial receipt for all other SAEs with AZ products. The clinical pharmacist will also report all follow-up information or corrections to data previously submitted on SAEs, within the same timelines specified for initial reporting, to the AZ representative. If a non-serious AE becomes serious, this and other relevant follow-up information is also provided to AstraZeneca within one day of initial receipt as described above.

6.4.2 Variables

The following variables will be collected for each adverse event with an AZ product;

- Adverse event (verbatim)
- The date when the adverse event started and stopped
- Maximum intensity
- Whether the adverse event is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to the AZ medication
- Whether the adverse event caused patient's withdrawal from study (yes or no) and
- Outcome

In addition, the following variables will be collected for SAEs:

- Date adverse event met criteria for an SAE

- Date Investigator became aware of an SAE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- In case of fatal reports:
- Probable cause of death,
- Date of death,
- Autopsy performed,
- Causality assessment in relation to study procedure(s), and
- Description of adverse event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

6.5 Overdose

An overdose is defined as a subject receiving a dose of an AstraZeneca product in excess of that specified in the US Prescribing Information unless otherwise prescribed by the physician.

Overdose in itself is not considered to be an AE or SAE.

If an overdose on an AZ product occurs in the course of the study, then the clinical pharmacist must inform appropriate AZ representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

For overdoses associated with a SAE with an AZ product, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

The following information should be provided in the event of an Overdose (Overdose Report Form can be provided upon request):

- Details of the Patient who was dispensed the AZ drug (Patient Identification number)

- Details of the Patient who took the overdose (demographic information, was patient a study participant?)

- Details of the drug overdose (total daily dose, route, formulation, Overdose start and stop dates)

- Was the overdose accidental or intentional?

- Was the overdose associated with an adverse event (serious or non-serious)

- Provide an Adverse Event description. Provide start and stop dates of the event, or indicate if the event is ongoing.

- Provide the Clinical Pharmacist's signature and date.

6.6 Pregnancy

If the clinical pharmacist is aware of a patient who becomes pregnant during the course of the study, the clinical pharmacist will request that the patient to seek advice from the patient's care physician on whether the potential benefit justifies the potential risk to the fetus, and whether the patient is still appropriate for continuation on the medication during pregnancy and any other relevant medical measures.

Pregnancy in itself is not considered to be an AE or SAE. However, the clinical pharmacist are responsible for recording and reporting pregnancies for patients using AZ products and their outcomes in accordance with the standard clinical study protocol instructions.

6.6.1 Maternal Exposure

If the clinical pharmacist is aware of a patient who becomes pregnant during the course of the study, the clinical pharmacist will request that the patient to seek advice from the patient's care physician on whether the potential benefit justifies the potential risk to the fetus, and whether the patient is still appropriate for continuation during pregnancy and any other relevant medical measures.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the AZ drug may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) while using any AZ product should be followed up and documented.

If any pregnancy occurs in the course of the study while using an AZ product, then the clinical informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ representative works with the clinical pharmacist to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see <<Section: Reporting of serious adverse events>>) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal Exposure

If paternal exposure pregnancy occurs in the course of the study while using an AZ product, then the clinical pharmacist should inform AZ within the same timeframe as the maternal exposure. The female partner of the patient will be asked to consent to allow collection of information and follow-up on the pregnancy. The outcome of the pregnancy is also followed and reported in accordance with the processes written in Section 6.6.1.

6.7 Management of IP related toxicities

N/A

6.8 Study governance and oversight

Due to the low-risk nature of this study, a data safety monitoring committee outside of the study team is not necessary.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

N/A

8. STATISTICAL ANALYSES

Overall strategic purpose of CSP Section 8: To confirm appropriateness of statistical methodology and assumptions, so that credibility of eventual clinical interpretation of the study data and conclusions will be enhanced.	
Physician representative	From a medical point of view, does the statistical approach address all the study objectives and will the analyses likely result in clinically meaningful and interpretable data to support the tollgate decision, proposed CDS and or TPP/TPCs? Has a robust clinical and statistical justification been provided for any non-inferiority/equivalence margins?

Overall strategic purpose of CSP Section 8: To confirm appropriateness of statistical methodology and assumptions, so that credibility of eventual clinical interpretation of the study data and conclusions will be enhanced.	
Biostatistics representative	Does the statistical approach address all the study objectives and will the analyses likely result in clinically meaningful and interpretable data to support the tollgate decision, proposed CDS and or TPP/TPCs? Has satisfactory statistical justification been provided for the choice of analysis methods (including any interim analyses), definition of analysis sets and calculations of sample size (including statistical and clinical justification for any non-inferiority/equivalence margins)? Could an independent statistician replicate the analyses?
Regulatory representative	Is the statistical approach in agreement with current regulatory guidelines and any outstanding Health Authority statistical concerns? Does this section highlight and adequately justify any lack of concordance with such guidelines and advice (noting any potential consequences for the proposed CDS)?

Statistical analyses will be conducted by the study team at [redacted] with input and review from the fully study team, including AstraZeneca and Horizon BCBSNJ team members.

8.1 Statistical considerations

Aim 1 (Primary Objective):

We have received Horizon Blue Cross Blue Shield Privacy Board approval to receive a HIPAA limited dataset on all patients for the purpose of analysis. The primary analyses will be conducted among all patients identified for the control group and the intervention group on an intention-to-treat basis. This approach will minimize the potential selection bias introduced by comparing only consenting patients to the identified controls, even if patients were carefully matched using observable covariates. Secondary analyses for all outcomes will be conducted among patients who provided informed consent versus the control group.

The primary outcome of interest will be the pre- to post-intervention change in mean HbA1c levels to the end of follow-up. Horizon BCBSNJ receives laboratory information from over 200 patient-centered medical homes and other population health programs and other practices. This laboratory information will be used to measure the change in HbA1c levels at the end of follow-up. 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.[24,25] We will use generalized estimating equations to compare the changes between the two study groups. Any observed imbalance between the groups will be controlled for using multivariable regression.

Secondary outcomes of interest include both glycemic outcomes and medication adherence outcomes. The secondary glycemic outcomes will include mean HbA1c levels at the end of follow-up and the proportion of patients achieving optimal glycemic control, defined as the proportion of patients who achieved a HbA1c <8.0%, which is the threshold for the most major quality measures used to assess the performance of health plans, including HEDIS. Patients' adherence to their diabetes medications will be measured by pharmacy claims and their filling patterns. For each medication, we will create a drug supply diary linking all observed fills after initiation based on dispensing date and days' supply. The supply for any early or overlapping fills can accumulate up to 180 days of excess supply in the supply diary. Different drugs in the same chemically-related therapeutic class (e.g., sulfonylureas) will be considered to be interchangeable. 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.[33] Using this PDC measure, we will observe the mean PDC in each study group and the proportion of patients achieving optimal adherence (defined by ≥0.80 PDC) as adherence outcomes in the follow-up period.

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 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).

Other medication adherence measurements will also be assessed, 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.[24,34]

Aim 2 (Secondary Objective):

As a secondary aim, we will use predictive analytics to examine whether the clinical outcomes could have been predicted based on patient factors, such as sociodemographic, clinical, medication use, and other motivational characteristics, 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.

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 regression models for patients in both the treatment and control groups, incorporating different patient characteristics as predictors. We will model these particular outcomes because these are considered to be clinically meaningful cutpoints 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 HbA1c and PDC and will include different numbers of predictor variables, in a method similar to previous work.[35,36] As predictors in these models, we will incorporate patients' baseline demographic, clinical, and medication use characteristics and information from the brief screening assessment during the initial pharmacist-delivered telephonic encounter. These baseline demographic, clinical, and medication use characteristics will be measured using Horizon BCBSNJ outpatient pharmaceutical, medical, and laboratory claims files. Some of the models will include only predictors available from administrative claims and not information from patient self-report. We will also assess the correlation between responses to the survey, baseline adherence as measured by pharmacy claims, and response to the intervention.

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 information and initial screening characteristics (e.g., Morisky score, PHQ-2 score, CHAI score). In addition, as initial filling information have been shown in previous work to be highly predictive of subsequent medication adherence, we will also include initial post-baseline filling information to assess the ability to predict medication adherence and glycemic control in the subsequent follow-up period.[35] 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.[37] 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.[38]

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.[21,22] 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) [39]. 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.[22]

The results of these predictive analytic efforts will help inform payers and providers about the types of patients who may respond to these patient engagement techniques. These findings will have specific ramifications for Horizon BCBSNJ as well as other payer organizations about how to manage their members who have poorly-controlled diabetes. We expect these results to also be generalizable to other chronic disease medication management programs.

8.2 Sample size estimate

We anticipate that identification of at least 700 individuals in the intervention group and control group should be sufficient to detect an average change of 0.5% in A1c, assuming an α=0.05, 1-β=0.80, A1c standard deviation=1.9, and a verbal informed consent rate of 45%, including clustering and non-differential loss-to-follow up between the study groups (Table 5). With this sample size, we should also have the ability to detect differences in the adherence outcomes (Table 6).

Based on feasibility information from Horizon, we anticipate that of the 315 patients in the intervention group who are likely to be reached by pharmacists (45%), at least 236 will have usable follow-up data. This proportion of reached patients has been observed in prior, pilot studies that have used a similar approach.[25] In order to observe an overall A1c difference of 0.5% in the study population, these contacted patients must have a underlying mean A1c change of ~0.49% (Figure 3). This difference is in line with what clinical guidelines consider to be a clinically meaningful difference in glycemic control. This A1c difference has been observed in prior work with clinical pharmacists.[8] This sample size would also provide enough patients for the predictive analytics work, given the relative non-rare nature of the study outcomes (glycemic control and medication adherence).

Table 5. Justification: A1c power calculation parameters and ranges

Range of parameters: input ranges	**A1c difference: 0.5%** **Sample size (N range)/group**
A1c SD: 1.9--> N_1	228
Intra-cluster correlation (N_2=N_1*1.03)	235
Loss-to-follow-up (LTF): 15-30%	(best case: 276, worst case: 335)

(N_3=N_2/[1-rate])	
Pharmacist contact rate: 35-50% (N_4=N_3/rate)	(best case: 552, worst case: 959)
Total	45% reach rate and 25% LTF: 696 patients/arm

Power (1-β): 0.80; Alpha (α): 0.05

Explanation of study parameters – Primary outcome (A1c)

- 1) Standard deviation of A1c: ranges between 1.0 and 2.0, depending on study length and average baseline A1c values. The most commonly cited value is 1.9, assuming equal variances between the groups. This would be non-differential between study groups.
- 2) Intra-cluster correlation: Other studies have also incorporated intra-cluster correlation (ICC) within PCP clinics (~0.03 for small pilot studies). This would be non-differential between study groups.
- 3) Loss-to-follow-up: Due to the potential for patients changing insurances particularly at the end of the calendar year, we anticipate that there could be some non-differential loss-to-follow-up of patients in the study. There may also be patients who do not have follow-up A1cs, despite restricting to patients whose providers have at-risk contracts with Horizon BCBS.
- 4) Pharmacist contact rate: We anticipate that approximately 45% of the patients will be reached by the pharmacists delivering the intervention.

Table 6. Justification: Adherence power calculation parameters and ranges

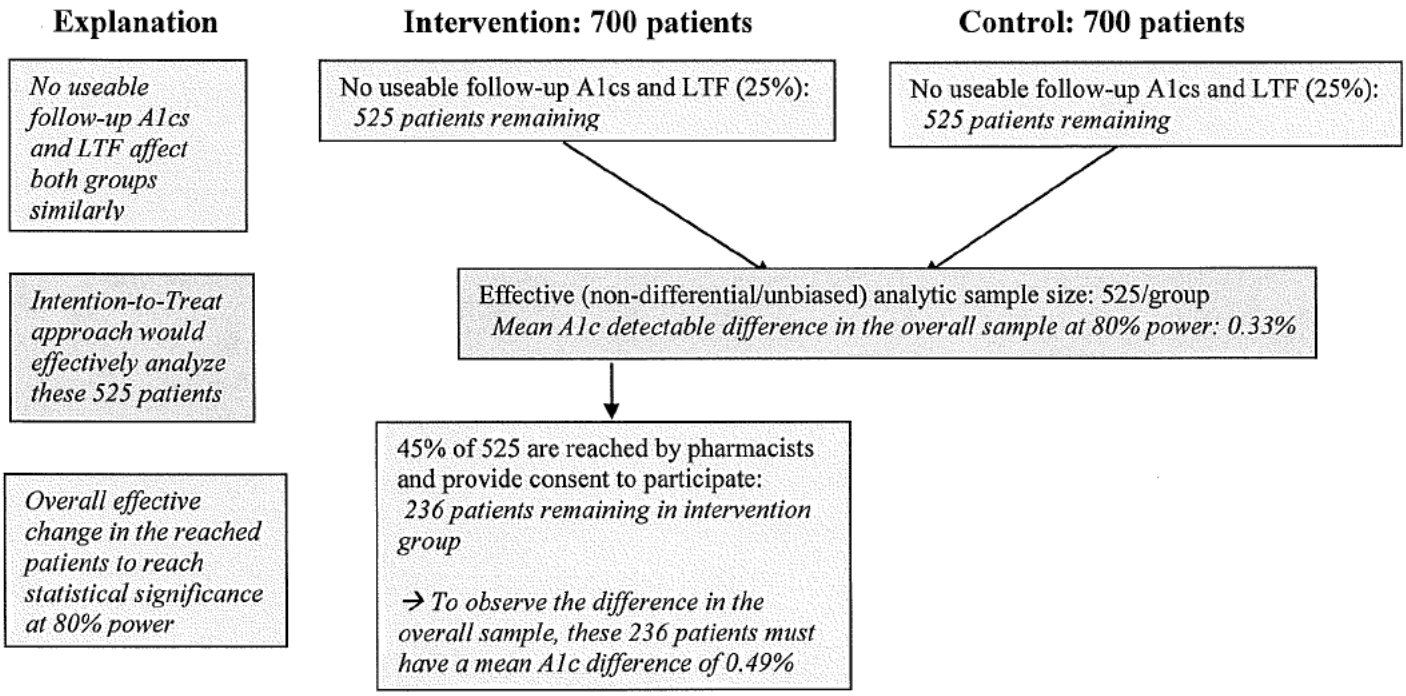
Range of parameters: input ranges	**Difference in mean PDC: 5% Sample size (N range)/group**
Baseline adherence: 50% --> N_1	253
Intra-cluster correlation (N_2=N_1*1.03)	261
Loss-to-follow-up (LTF): 10-25% (N_3=N_2/[1-rate])	(best case: 290, worst case: 347)
Pharmacist contact rate: 35-50% (N_4=N_3/rate)	(best case: 580, worst case: 993)
Total	45% reach rate and 15% LTF: 682 patients/arm

Power (1-β): 0.80; Alpha (α): 0.05

Explanation of additional study parameters – Secondary outcome (Adherence)

- 1) Baseline adherence:
  - 5% absolute difference in mean PDC has been seen in previous intervention studies and is considered to be a clinically meaningful difference[16,24]
  - Assuming ~50% baseline adherence based on previous literature[24]
- 2) Loss-to-follow-up: Due to the potential for patients changing insurances, we anticipate there could be some non-differential loss-to-follow-up of patients in the study. Prescription claims will be captured on all patients included in the study by definition, enabling the calculation of adherence until loss of continuous eligibility.

Figure 3. Schematic of analytic plan



8.3 Definitions of analysis sets

The full analysis set (Intention-to-Treat principle) will be used for the study analysis.

8.4 Outcome measures for analyses

Please see Section 8.1 for further detail.

8.5 Methods for statistical analyses

Please see Section 8.1 for further detail.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all study staff involved in the study. The Principal Investigator will also train the clinical pharmacists at [redacted] in the conduct of the intervention, in accordance with the study timeline.

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study investigators:

- Provide information and support to the Investigator(s)
- Confirm that the investigational team is adhering to the protocol

The AstraZeneca representative will be available as necessary if the Investigator(s) or other staff need information and advice about the study conduct.

9.2.1 Source data

N/A

9.2.2 Study agreements

The Principal Investigator should comply with all the terms, conditions, and obligations of the Clinical Study Protocol, or equivalent, for this study. Patients' physicians will be communicated with by the study pharmacists, and all treatment plans and changes will ultimately be approved by patients' own prescribing physicians.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Protocol.

9.2.4 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and AstraZeneca or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the AstraZeneca, the name/department name of the study site, the address or phone number of the study site or AstraZeneca, the job title of the Investigator, and monitors).

9.3 Study timetable and end of study

The study is expected to start in Quarter 3 2016 and to end by Quarter 2 2017. Recruitment will begin and end in Quarter 3 2016.

Completion of the study

Upon terminating the study, the Principal Investigator/Investigator will report in writing the completion of the study to the IRB and AstraZeneca.

9.4 Data management by [redacted] and Horizon Analytics

Data management will be primarily performed by Horizon Analytics and secondarily by [redacted] Data queries will be raised for inconsistent, impossible or missing data. Horizon Analytics will disclose a very limited set of Protected Health Information (PHI)/data to the study partners, mainly to the [redacted] pharmacists to conduct the intervention (similar to data already shared with [redacted] for other Horizon outreach efforts). All data will be transferred by Horizon using a File Transfer Protocol (FTP) site from Horizon in accordance with current practices. Horizon uploads PHI/data and only one designated person at each site will securely log in using a designated username and password and download data to local, secure servers.

[redacted] The study patients will be identified by Horizon Analytics for [redacted] These data will be similar to data that are routinely shared with [redacted] already for other outreach interventions to Horizon members. The PHI/data will be the minimum necessary for the intervention and include the following information: demographic information, contact information, pharmacy contact information, primary care provider/practice, pharmacy claims information, and laboratory information. This information will be necessary to intervene upon eligible patients.

[redacted] The PHI that will be disclosed by Horizon to the aforementioned study partners at the [redacted] include a limited dataset that includes dates but no other identifying information, encrypted by a study key only known to Horizon, as follows: age, sex, pharmacy claims information, laboratory information, and medical claims. This information will be necessary to assess the impact of the intervention.

The data will be stored on password-protected servers at each of the entities participating in the study. Additionally, all personnel with access to Horizon data will have had recent training in HIPAA privacy and security policies. All data will be transferred by Horizon using a FTP site from Horizon and unstructured, segmented ASCII datafiles to be maintained within traditional database/data warehouse environments (to [redacted]) and Excel datafiles (to [redacted] in accordance with current practices for outreaches) using the minimum number of files necessary. All data analysis will be performed within these traditional database environments so that privacy and security from unstructured data will be maintained. Data will not leave the controlled server, and any information brought out of these secure environments and files provided by Horizon will only be in aggregated form and will not contain any individual PHI. The data files will remain on the secure server under password protection and no datafiles will reside on local computers. In addition, access will only be maintained for the exact period necessary to conduct the work.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

When all data have been validated and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

As previously described in Section 3.10, we have received a waiver of authorization for Horizon to share PHI with [redacted] for the purpose of the intervention and for Horizon to share a HIPAA limited dataset with [redacted] to conduct analyses on all identified intervention and control patients. The intervention itself poses no more than minimal risk because of the extensive security and privacy measures undertaken by the study team; any treatment decisions are also still being made by the patients' own physicians.

10.3 Ethics and regulatory review

An Institutional Review Board (IRB) from the [redacted] will approve the final study protocol, including any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB Committee, and to the study site staff.

The opinion of the IRB Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any subject into the study. If required by local regulations, the protocol should be re-approved by the IRB Committee annually.

10.4 Informed consent

[redacted] will obtain verbal informed consent from patients prior to administering the intervention. All calls with patients, including those in which this consent is obtained, will be recorded and available for auditing.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

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Clinical Study Protocol Appendix A	
Drug Substance	NA
Study Code	D1843R00254
Edition Number	2
Date	October 17, 2016
Protocol Dated	October 17, 2016

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

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

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Developme
site representative

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SIGNATURE OF PRINCIPAL INVESTIGATOR

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

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this amendment.

Centre No.:

Signature:

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