Targeted Adherence Intervention to Reach Glycemic Control With Insulin Therapy for Patients With Diabetes (TARGIT-DM)

NCT02846779

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Initial protocol

Targeted Adherence Intervention to Reach Glycemic Control with Insulin Therapy for patients with Diabetes (TARGIT-DIABETES)

OBJECTIVES

Primary aim: To evaluate the impact of three intervention strategies of equivalent cost but which vary by degree of targeting and intervention intensity, on insulin persistence (primary outcome) and HbA1c level (secondary outcome) at 12 months.

Secondary aim: To compare rates of healthcare utilization and spending between treatment groups, including diabetes-specific clinic visits, and emergency room visits.

BACKGROUND AND SIGNIFICANCE

With over 25 million Americans affected and annual costs upwards of $174 billion, diabetes remains a national public health priority.[1] Effective medications to control blood glucose and reduce the morbidity associated with this condition are widely available and uptake in the past decade has been encouragingly high. In 2011, the age-adjusted percentage of adults with diagnosed diabetes who reported taking oral hypoglycemic therapy, insulin, or both was nearly 81%.[2]

Unfortunately, non-adherence to these evidence-based therapies is extremely common and is a central contributor to poor diabetic outcomes, including cardiovascular decline, kidney, eye, and nerve disease complications.[3] Non-adherence to oral hypoglycemic medications, typically the first line of therapy after diagnosis, remains around 50%, while self-reported non-adherence to insulin is as low as 30%.[4,5] Among diabetic patients initiating basal insulin, treatment persistence, defined as remaining on the initial prescribed insulin without switching or discontinuation, at 12 months is 65%.[6]

To date, research to characterize non-adherence to insulin and evaluate interventions to improve uptake and promote appropriate and consistent use remains sparse. Given the growing numbers of patients on insulin and the significant barriers to adherence among patients on insulin, including inconvenience, embarrassment, lifestyle restriction, negative social stigma, and poor self-efficacy, more research in this domain is urgently needed.

Successful interventions must be multi-faceted and thus are often complex. When considering large-scale system-wide interventions, complexity is not a virtue. Moreover, there may be significant inefficiencies to providing adherence interventions to patients who may not need or benefit from them. To improve the

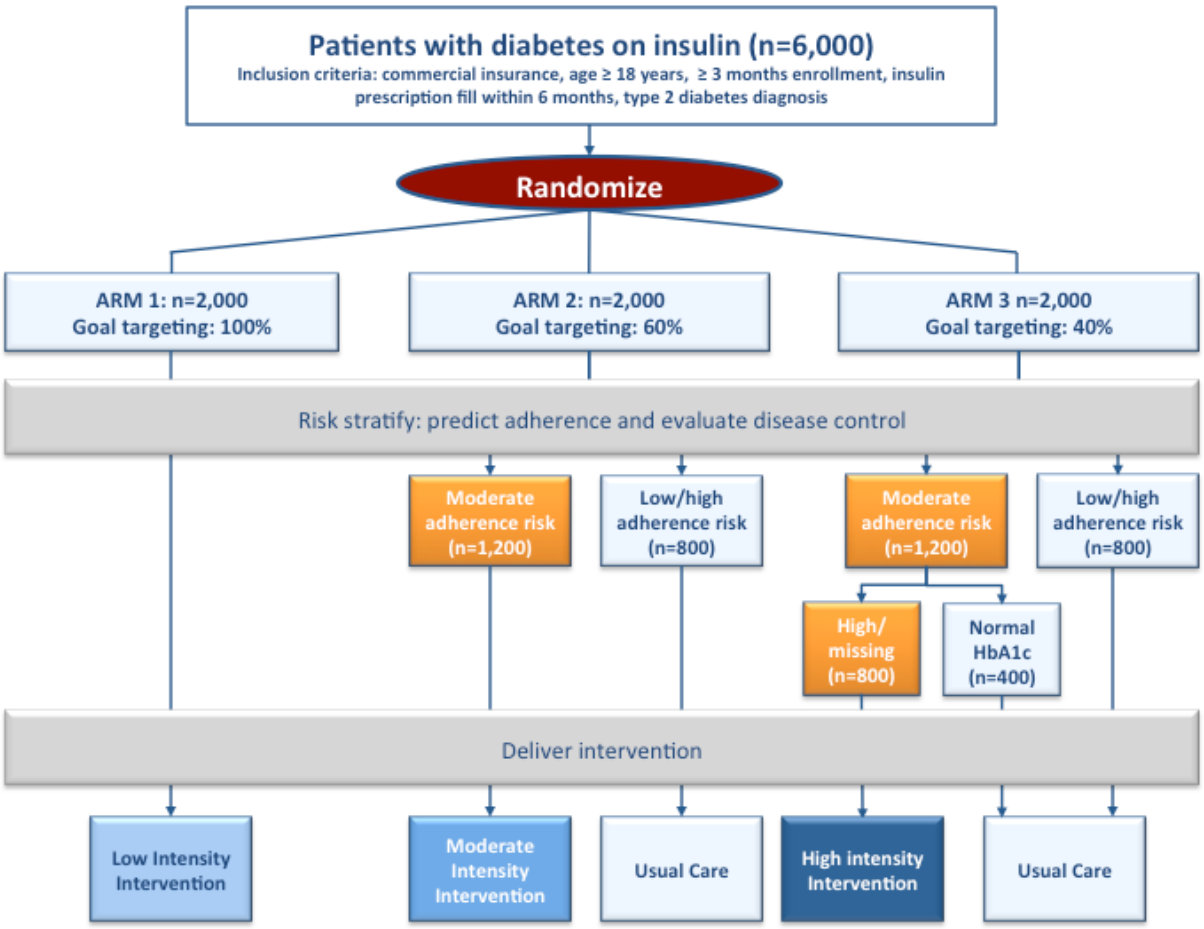
likelihood that interventions will be feasible on a large scale and can be transferred between sites, multi-faceted yet targeted interventions are warranted.

The primary aim of this study is to compare three equivalently priced strategies for improving insulin persistence and glycosylated hemoglobin [HbA1c] control among diabetic patients on insulin. The three study arms will use interventions that differ both with regard to which patients are targeted and the intensity of the engagement strategy that will be used (see Figure 1). The low intensity intervention in study arm 1 will be deployed to all subjects randomized to that arm while a moderate intensity intervention will be deployed to focused populations within study arm 2 and a high intensity intervention will be deployed to an even more focused population in study arm 3. The targeted population will be defined through poor disease control and/or predicted risk of non-adherence. We will evaluate differences in rates medication persistence measures and changes in HbA1c between the study arms using routinely collected data.

The study population for this trial will consist of members enrolled in commercial insurance provided by Horizon Blue Cross Blue Shield of New Jersey (Horizon), one of the largest health insurers in New Jersey. Horizon has demonstrated a strong commitment to quality improvement interventions for patients with chronic diseases and has previously worked with Dr. Choudhry and his colleagues to recruit members to participate in pragmatic clinical trials.

Horizon has an internal Privacy Board whose mandate is to review the risks and anticipated benefits to Horizon members of any proposed research project and to assure that research projects guarantee the privacy of members and confidentiality of data. For the current study, the Privacy Board has reviewed and approved the proposed trial as described herein and has provided a waiver of HIPAA authorization to use Horizon data for subject identification.

Figure 1: Overall Study Design



STUDY DESIGN

The proposed three-arm pragmatic trial will employ quality improvement interventions currently in use by Horizon but which, for the purposes of this study, will differ both with regard to which patients are targeted and the intensity of the engagement strategy that will be used. Because the cost of each arm is equivalent, arms without targeting will provide a lower cost, less intensive intervention to a greater number of patients, whereas arms with patient targeting will be able to provide a more intensive intervention to fewer patients who are deemed to be at risk. Please see Figure 1 for a schematic of the three study arms.

ARM 1: Non-Targeted Low Intensity Intervention

All patients in this arm will receive a low intensity, telephonic clinical pharmacist-lead adherence intervention, as described in the following section. The intervention will be offered to all patients regardless of adherence risk prediction or disease control. Because the intervention will be deployed to all subjects in

the arm, the nature of the intervention will be less intense, such that the number of phone calls will be limited and the resources offered will occur primarily at the beginning of the intervention period.

ARM 2: Adherence Risk-Targeted Moderate Intensity Intervention

Patients who are at moderate risk of insulin non-adherence at the start of the study, as determined by an external data analytics company that currently works with Horizon, RxAnte, will receive a moderate intensity adherence intervention. Sixty percent of patients will be targeted (hereafter referred to as “high-value” targeting) and receive the intervention. Patients predicted to have a very high or very low risk of non-adherence (low-value targeting) will receive usual care. Because the intervention will be deployed to fewer subjects in the arm, the nature of the intervention will be more intense. Not only will patients be able to receive more pharmacist phone calls, the clinical pharmacist will be able to offer more resources to assist with adherence and will also provide limited feedback as necessary to the patient’s providers, including the prescribing physician and/or pharmacist.

ARM 3: Adherence Risk and Glycemic Control-Targeted High Intensity Intervention

This arm uses both adherence risk assessment as well as glycemic control, as assessed by baseline levels of HbA1c, to determine which patients are targeted and which intervention they receive. Patients will be targeted if they have a) moderate risk of non-adherence and b) poor disease control (HbA1c ≥ 8%) or unknown control (missing HbA1c). Overall, 40% of patients will be targeted (high-value targeting) and receive the intervention; the rest will receive usual care.

Because the number of patients receiving the intervention is less than in arm 2, the nature of the intervention will be even more intense. Patients will receive more telephone calls and the clinical pharmacist will be able to offer much more outreach to the patient’s prescribing physician and/or pharmacist.

Table: Type of targeting and intervention assignment in each arm

Targeting Approach	Arm 1	Arm 2	Arm 3
Sample size	2000	2000	2000
Targeting rate	100%	60%	40%
Number targeted	2000	1200	800
Type of targeting	None	Adherence risk only	Adherence risk and Glycemic control
Intervention	Low intensity	Moderate intensity for patients with moderate adherence risk	High intensity for patients with moderate adherence risk AND high/unknown HbA1c

Adherence risk prediction

Adherence risk will be determined at the start of the study in partnership with RxAnte, whose analytics platform uses standard insurer enrollment and claims data to predict future medication use. RxAnte has a pre-existing relationship with Horizon and performs adherence risk prediction analytics for patients with chronic diseases such as hypertension and diabetes.

The company's algorithm assigns patient-level scores to reflect adherence predictions and has previously been validated to predict non-persistence to insulin. RxAnte will create a validation cohort with the Horizon claims data from 2013-2015 and will prospectively apply this model to the 2016 Horizon enrollment data. For the purpose of this study, our goal is to intervene on 60% patients in arm 2 and 40% patients in arm 3. Therefore we will assign a clinically-meaningful threshold within which we will target patients.

Patients who are assessed to have a very high or very low risk of non-adherence (the highest and lowest risk scores) will be considered to be low-value targets. Our hypothesis is that these patients are unlikely to benefit from an adherence intervention due to ongoing very poor or very good adherence, respectively. This reflects current clinical practice of who is targeted with quality improvement interventions at the level of large insurers. Patients who are assessed to have a moderate risk of non-adherence will be considered to be high-value targets. These are patients with an adherence risk score of 0.2 and higher (20% probability or higher of being adherent to insulin at 12 months).

INTERVENTION COMPONENTS

The interventions for each of the study arms will be delivered by Magellan, a pharmacy benefit management company that provides telephonic disease management services to numerous large insurers, including Horizon. The specific interventions have been designed by the investigative team in conjunction with

Magellan and will offer an approach tailored to increasing levels of patient engagement and support in attaining higher levels of insulin persistence.

The intervention components increase in frequency and type of contact across the three study arms and are cumulative (each arm includes all intervention components included in previous arm). Each patient will receive an introductory mailing that describes the pharmacist consultation and a pillbox. The components are summarized in the table below and described in more detail in Appendix B.

Table: Summary of intervention components

Intervention Components	Arm 1	Arm 2	Arm 3
Outreach Population (n)	2000	1200	800
Introductory mailing with pillbox	X	X	X
Telephonic intervention focus	Adherence	Adherence and Glycemic Control	Adherence and Glycemic Control
Max number of calls to patient	4	6	12
Type of provider and/or pharmacy outreach	Obtain contact information	Obtain contact information; limited f/u from techs/CCAs for certain clinical scenarios	Obtain contact information; full f/u from techs/CCAs/ PharmDs for all clinical scenarios
Max number of calls to provider/pharmacist	1	2	12
Quarterly educational mailings		X	X
Text messaging (TM) service	None	Moderate intensity	High intensity

ARM 1: Non-Targeted Low Intensity Intervention

Patients will receive an adherence outreach delivered by Magellan clinical staff, including pharmacists with or without advanced training (e.g. certification in Medication Therapy Management), nurses, technicians, customer care associates, and 4th year PharmD candidates. Patients will be contacted by telephone and during these calls, the Magellan staff will:

1. Confirm current treatment regimen and reason(s) for treatment

2. Guide member-specific discussion focused on identifying potential barriers to medication adherence including cost, side effects, complexity of regimen, education, and expectations of treatment

3. Conduct motivational interviewing and educational reinforcement regarding disease state, importance of adherence, and strategies for success/improvement.

This telephonic consultation may be repeated up to 2 times (3 calls total) and will focus on identifying and overcoming barriers to adherence. The follow-up calls may be limited to the beginning of the outreach and will not necessarily be distributed throughout the duration of follow-up.

ARM 2: Adherence Risk-Targeted Moderate Intensity Intervention

Patients will receive an adherence and glycemic control outreach delivered by Magellan clinical staff. Only members with a telephone number available in the Horizon member files will be assigned to the moderate intensity intervention. Patients will be contacted by telephone and during these calls, in addition to the topics discussed in arm 1, the Magellan staff will:

1. Assess the adequacy of the patient's regimen. Staff will not suggest any changes to the patient's regimen but instead educate and encourage patient to communicate to provider.

2. Guide member-specific discussion focused on identifying potential barriers to glycemic control including availability of glucose monitoring equipment, side effects, barriers to diet and lifestyle recommendations, and education

3. Conduct motivational interviewing and educational reinforcement regarding disease state, importance of adherence, and strategies for success/improvement

In addition to the pharmacist intervention described in arm 1, this arm will include:

- Up to 6 calls total by Magellan clinical staff. If 6 calls are not deemed necessary by patient and pharmacist, the pharmacist will at the very least try to provide follow-up at 3, 6, and 9 months after randomization, where appropriate.

- One outreach call to provider or pharmacist, as needed, to update clinical status and resolve potential barrier to adherence

- Referral to a moderate intensity text messaging (TM) service as needed. The content of the TMs have been created by the BWH investigators and the TMs themselves will be delivered by the investigators to a Magellan subcontractor, Mobile Commons, which provides a service for patients to provide their cell phone numbers to receive weekly text messages in a way that is confidential. Patients will be asked to opt in.

- Quarterly follow-up letters at 3, 6, and 9 months that include information about importance of glycemic control and adherence. The schedule of mailings is listed in the table below and copies of the actual mailings are attached.

Table: Mailings schedule

Month	Arm 1	Arms 2 and 3	
0	Intro letter and postcard + pillbox	Intro letter and postcard + pillbox	Intro letter and postcard + pillbox
		Previously reached by Magellan pharmacist	Previously not reached by Magellan pharmacist
3		• Follow-up letter: previously reached member • Handout: "Understanding my insulin treatment"	• Follow-up letter: previously not reached member • Handout: "Understanding my insulin treatment"

6	• Follow-up letter: previously reached member • Handout: “Remembering to take my medicines”	• Follow-up letter: previously not reached member • Handout: “Remembering to take my medicines”
9	• Follow-up letter: previously reached member • Handout: “Maintaining my treatment plan”	• Follow-up letter: previously not reached member • Handout: “Maintaining my treatment plan”

ARM 3: Adherence Risk and Glycemic Control-Targeted High Intensity Intervention

Patients will receive the same adherence and glycemic control outreach delivered by Magellan clinical staff as described in Arm 2. Only members with a telephone number available in the Horizon member files will be assigned to the high intensity intervention.

In addition to the pharmacist interventions described in arm 2, this arm will include the following changes:

- Up to 12 calls total by Magellan clinical staff, instead of 6 calls total.

- Up to 12 outreach calls to provider or pharmacist, as needed, to update clinical status and resolve potential barrier to adherence, instead of 1 outreach call. In this scenario, the pharmacist may discuss potential insulin dose titration with prescribing physician and communicate these changes back to the patient with the provider’s permission.

- Referral to a high intensity text messaging (TM) service as needed, instead of referral to only a moderate TM service. The moderate intensity TM service includes weekly texts whereas the high intensity TM service includes daily texts. Patients will have the option to enroll in either frequency, if interested. If the patient elects into receiving daily texts, they will have the option of switching into weekly texts or no texts at any point during the intervention.

STUDY POPULATION

Patients who are potentially eligible for inclusion will be identified from the cohort of patients currently receiving health insurance from Horizon. In order to maintain generalizability, exclusion criteria will be minimal. Patients meeting the following inclusion/exclusion criteria will be selected for participation:

Inclusion criteria:

a) Commercially-insured individuals who receive medical and pharmacy health insurance benefits administered by Horizon Blue Shield Blue Cross of New Jersey
b) Age ≥ 18 years as of January 1, 2016
c) ≥ 3 months of continuous enrollment prior to randomization

d) ≥ 1 prescription for basal insulin during the 6 months prior to randomization
e) Members with type 2 diabetes, as determined by medical claims or prior prescription of an oral anti-diabetic medication (OAD)

Exclusion criteria:

a) Patients whose primary insurance is Medicaid or Medicare

Baseline HbA1c will not be an inclusion criterion. However patients with baseline HbA1c (within 6 months of randomization) will be flagged and later stratified during randomization.

RECRUITMENT PROCEDURE

Patients will be recruited into the study by a review of Horizon medical and pharmacy claims and risk scoring performed by RxAnte. After randomization, patients will be assigned to an intervention group or usual care depending on study arm, adherence risk score, and baseline HbA1c value.

Once a patient is reached, the Magellan pharmacist will explain the purpose of the consultation and ask the patient if he/she would like to participate. If a patient agrees, this will be considered implicit consent. If a patient wishes to not participate and wishes to not receive further contact, this will be noted and the patient will not be contacted again.

Data on all patients will be analyzed according to whichever group the patient was randomized to, regardless of whether the patient was reached or agreed to participate.

RANDOMIZATION

There are multiple partners who are working together to identify eligible patients and deliver the intervention. Our goal is to use the minimal amount of clinical data necessary at each step in order to implement the intervention. Because of the large number of patients who will be contacted by Magellan pharmacists, patient selection, randomization, and recruitment will occur over the first 4 months of the trial. This will require the following steps:

- Horizon analytics team will send claims data on all insulin users from 2013 to 2015 to RxAnte to perform validation of insulin adherence risk scores. Before the study starts, Horizon will send updated enrollment files.
- RxAnte will assign risk scores on all insulin users and send risk scores to Horizon
- Horizon will apply inclusion and exclusion criteria and select patients eligible for randomization. They will flag patients with baseline HbA1c values, claims-based diabetes diagnosis (in contrast to OAD-based diabetes diagnosis, and telephone number availability).

- Horizon will randomize 1,500 patients meeting criteria above. Randomization will be stratified by HbA1c availability, claims-based diabetes diagnosis, and telephone number availability.
- Horizon will send the following aggregated and de-identified data to Brigham: distribution of risk scores and HbA1c values in arms 2 and 3. Brigham investigators will choose risk score and HbA1c cut-offs that will result in appropriate targeting levels.
- Brigham will send these cut-offs to Horizon. The Horizon analytics team will apply these thresholds to make intervention assignments within each randomized group.
- Horizon will send the necessary data on all patients assigned to receive an intervention to Magellan.
- The process above will be repeated monthly 3 additional times so that randomized and recruitment is staggered over the course of 4 months.

Randomization will occur in a 1:1:1 ratio conducted on the patient level. In order to have adequate power to study our secondary outcome, change in HbA1c, our randomization will be stratified on patients with baseline HbA1c lab availability within the 6 months prior to randomization.

This randomization will occur using a random number generator at Horizon Analytics. Randomization codes will be assigned strictly sequentially as patients become eligible. The randomization key will be maintained at Horizon Analytics as well as the allocation of patients to the intervention arms.

Data Sources

The data that will be used for patient selection and analysis includes medical and pharmacy claims and lab data from Horizon. Complete paid pharmacy and medical services claims data will be combined into a database consisting of all filled prescription, procedures, inpatient and outpatient physician encounters, hospitalizations, long-term care admissions and deaths for all patients studied.

In addition to the Horizon claims data, both vendors will provide de-identified aggregate data on risk prediction and patient contact to Brigham investigators. Specifically, RxAnte will provide aggregate risk prediction scores from their initial scoring. These scores will be linked to an anonymous patient ID (the link between patient ID and medical record number will be kept by Horizon analytics). Magellan will provide a monthly report of how many patients were reached and the type of contact (e.g. number of patients who were engaged on the telephone, the number of providers who were contacted).

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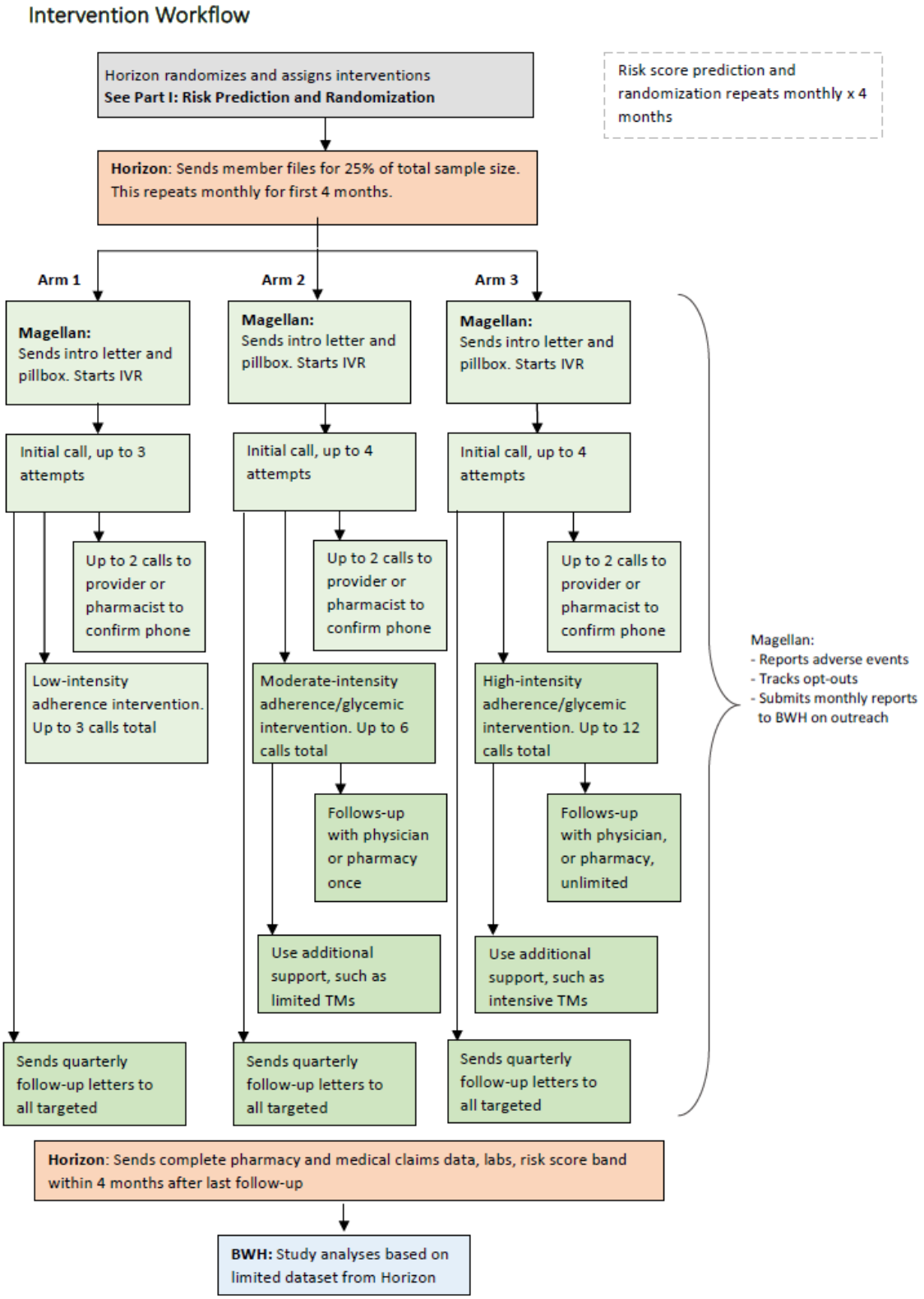
Appendix B: Study Workflow



Final protocol

Targeted Adherence Intervention to Reach Glycemic Control with Insulin Therapy for patients with Diabetes (TARGIT-DIABETES)

OBJECTIVES

Primary aim: To evaluate the impact of three intervention strategies of equivalent cost but which vary by degree of targeting and intervention intensity, on insulin persistence (primary outcome) and HbA1c level (secondary outcome) at 12 months.

Secondary aim: To compare rates of healthcare utilization and spending between treatment groups, including diabetes-specific clinic visits, and emergency room visits.

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With over 25 million Americans affected and annual costs upwards of $174 billion, diabetes remains a national public health priority.[1] Effective medications to control blood glucose and reduce the morbidity associated with this condition are widely available and uptake in the past decade has been encouragingly high. In 2011, the age-adjusted percentage of adults with diagnosed diabetes who reported taking oral hypoglycemic therapy, insulin, or both was nearly 81%.[2]

Unfortunately, non-adherence to these evidence-based therapies is extremely common and is a central contributor to poor diabetic outcomes, including cardiovascular decline, kidney, eye, and nerve disease complications.[3] Non-adherence to oral hypoglycemic medications, typically the first line of therapy after diagnosis, remains around 50%, while self-reported non-adherence to insulin is as low as 30%.[4,5] Among diabetic patients initiating basal insulin, treatment persistence, defined as remaining on the initial prescribed insulin without switching or discontinuation, at 12 months is 65%.[6]

To date, research to characterize non-adherence to insulin and evaluate interventions to improve uptake and promote appropriate and consistent use remains sparse. Given the growing numbers of patients on insulin and the significant barriers to adherence among patients on insulin, including inconvenience, embarrassment, lifestyle restriction, negative social stigma, and poor self-efficacy, more research in this domain is urgently needed.

Successful interventions must be multi-faceted and thus are often complex. When considering large-scale system-wide interventions, complexity is not a virtue. Moreover, there may be significant inefficiencies to

providing adherence interventions to patients who may not need or benefit from them. To improve the likelihood that interventions will be feasible on a large scale and can be transferred between sites, multi-faceted yet targeted interventions are warranted.

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The study population for this trial will consist of members enrolled in commercial insurance provided by Horizon Blue Cross Blue Shield of New Jersey (Horizon), one of the largest health insurers in New Jersey. Horizon has demonstrated a strong commitment to quality improvement interventions for patients with chronic diseases and has previously worked with Dr. Choudhry and his colleagues to recruit members to participate in pragmatic clinical trials.

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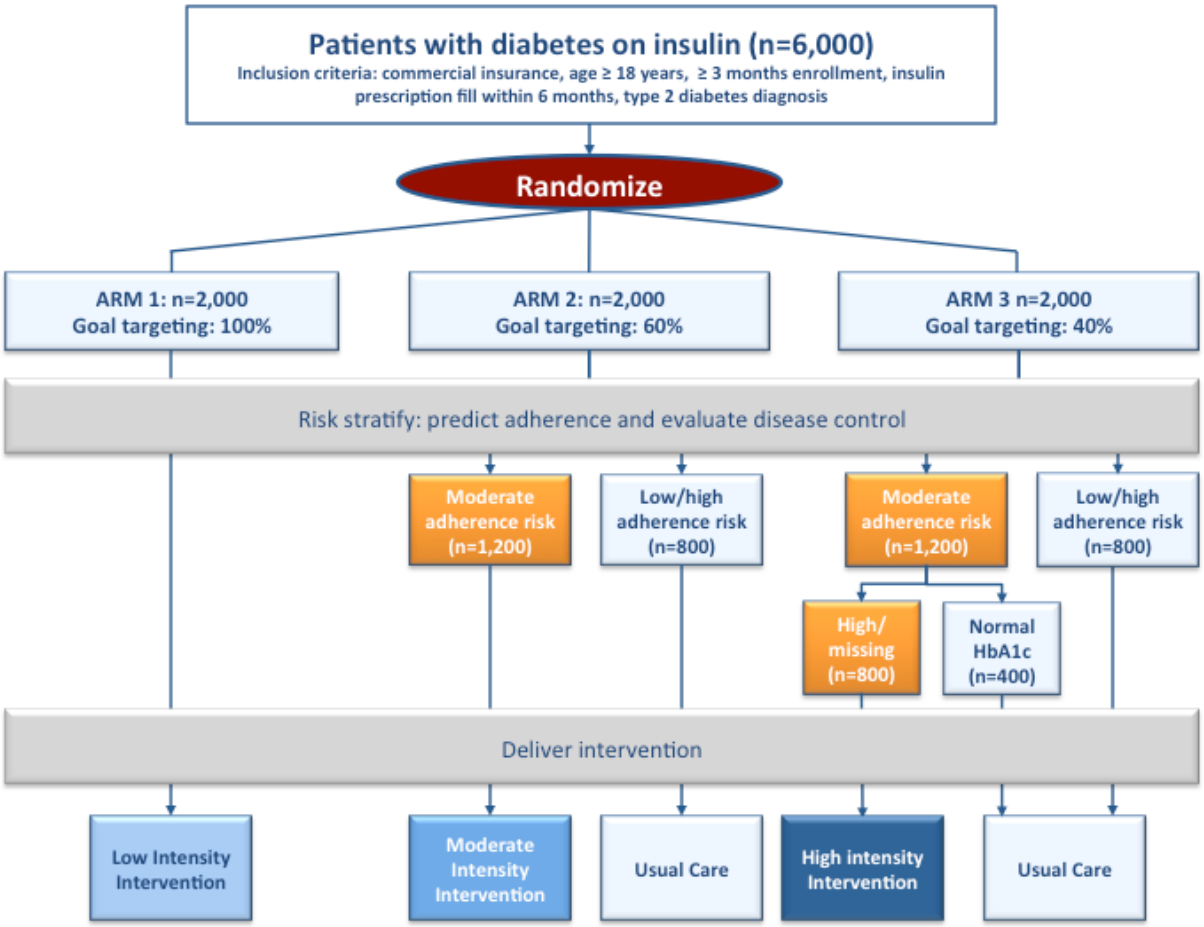

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ARM 2: Adherence Risk-Targeted Moderate Intensity Intervention

Patients who are at moderate risk of insulin non-adherence at the start of the study, as determined by an external data analytics company that currently works with Horizon, RxAnte, will receive a moderate intensity adherence intervention. Sixty percent of patients will be targeted (hereafter referred to as “high-value” targeting) and receive the intervention. Patients predicted to have a very high or very low risk of non-adherence (low-value targeting) will receive usual care. Because the intervention will be deployed to fewer subjects in the arm, the nature of the intervention will be more intense. Not only will patients be able to receive more pharmacist phone calls, the clinical pharmacist will be able to offer more resources to assist with adherence and will also provide limited feedback as necessary to the patient’s providers, including the prescribing physician and/or pharmacist.

ARM 3: Adherence Risk and Glycemic Control-Targeted High Intensity Intervention

This arm uses both adherence risk assessment as well as glycemic control, as assessed by baseline levels of HbA1c, to determine which patients are targeted and which intervention they receive. Patients will be targeted if they have a) moderate risk of non-adherence and b) poor disease control (HbA1c ≥ 8%) or unknown control (missing HbA1c). Overall, 40% of patients will be targeted (high-value targeting) and receive the intervention; the rest will receive usual care.

Because the number of patients receiving the intervention is less than in arm 2, the nature of the intervention will be even more intense. Patients will receive more telephone calls and the clinical pharmacist will be able to offer much more outreach to the patient’s prescribing physician and/or pharmacist.

Table: Type of targeting and intervention assignment in each arm

Targeting Approach	Arm 1	Arm 2	Arm 3
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Intervention	Low intensity	Moderate intensity for patients with moderate adherence risk	High intensity for patients with moderate adherence risk AND high/unknown HbA1c

Adherence risk prediction

Adherence risk will be determined at the start of the study in partnership with RxAnte, whose analytics platform uses standard insurer enrollment and claims data to predict future medication use. RxAnte has a pre-existing relationship with Horizon and performs adherence risk prediction analytics for patients with chronic diseases such as hypertension and diabetes.

The company's algorithm assigns patient-level scores to reflect adherence predictions and has previously been validated to predict non-persistence to insulin. RxAnte will create a validation cohort with the Horizon claims data from 2013-2015 and will prospectively apply this model to the 2016 Horizon enrollment data. For the purpose of this study, our goal is to intervene on 60% patients in arm 2 and 40% patients in arm 3. Therefore we will assign a clinically-meaningful threshold within which we will target patients.

Patients who are assessed to have a very high or very low risk of non-adherence (the highest and lowest risk scores) will be considered to be low-value targets. Our hypothesis is that these patients are unlikely to benefit from an adherence intervention due to ongoing very poor or very good adherence, respectively. This reflects current clinical practice of who is targeted with quality improvement interventions at the level of large insurers. Patients who are assessed to have a moderate risk of non-adherence will be considered to be high-value targets. These are patients with an adherence risk score of 0.1 and higher (10% probability or higher of being adherent to insulin at 12 months).

Once RxAnte calculates baseline risk scores on the entire population, we will look at the distribution of risk scores in arms 2 and 3 to make intervention assignments. In arm 2, we will assign the moderate intensity intervention to all patients with a telephone number with a risk score of 0.1 up until the point where we reach 60% of the population (1200 patients). All other patients in arm 2 will receive usual care. In arm 3, we will assign the high intensity intervention to all patients with a telephone number with a HbA1c greater than or equal to 8% or missing HbA1c who have a risk score of 0.2 or greater, up until the point where we reach 40% of the population (800 patients). All other patients in arm 3 will receive usual care.

INTERVENTION COMPONENTS

The interventions for each of the study arms will be delivered by Magellan, a pharmacy benefit management company that provides telephonic disease management services to numerous large insurers, including Horizon. The specific interventions have been designed by the investigative team in conjunction with Magellan and will offer an approach tailored to increasing levels of patient engagement and support in attaining higher levels of insulin persistence.

The intervention components increase in frequency and type of contact across the three study arms and are cumulative (each arm includes all intervention components included in previous arm). Each patient will receive an introductory mailing that describes the pharmacist consultation and a pillbox. The components are summarized in the table below and described in more detail in Appendix B.

Table: Summary of intervention components

Intervention Components	Arm 1	Arm 2	Arm 3
Outreach Population (n)	2000	1200	800
Introductory mailing with pillbox	X	X	X
Telephonic intervention focus	Adherence	Adherence and Glycemic Control	Adherence and Glycemic Control
Outreach based on telephone number availability	All members	Only members with phone number	Only members with phone number
Max number of attempts to engage patient	3	4	4
Max number of calls to engaged patient	3	6	12
Type of provider and/or pharmacy outreach	Obtain contact information	Obtain contact information; limited f/u from techs/CCAs for certain clinical scenarios	Obtain contact information; full f/u from techs/CCAs/ PharmDs for all clinical scenarios
Max number of calls to provider/pharmacy for contact info	2	2	2
Max number of pharmacy/provider clinical follow-up	0	1	12
Quarterly educational mailings	None	X	X
Text messaging (TM) service	None	Moderate intensity	High intensity
Adverse event reporting	X	X	X

ARM 1: Non-Targeted Low Intensity Intervention

Patients will receive an adherence outreach delivered by Magellan clinical staff, including pharmacists, nurses, technicians, customer care associates, and 4th year PharmD candidates. Patients will be contacted by telephone and during these calls, the Magellan staff will:

4. Confirm current treatment regimen and reason(s) for treatment

5. Guide member-specific discussion focused on identifying potential barriers to medication adherence including cost, side effects, complexity of regimen, education, and expectations of treatment

6. Conduct motivational interviewing and educational reinforcement regarding disease state, importance of adherence, and strategies for success/improvement.

This telephonic consultation may be repeated up to 2 times (3 calls total) and will focus on identifying and overcoming barriers to adherence. The follow-up calls may be limited to the beginning of the outreach and will not necessarily be distributed throughout the duration of follow-up.

Magellan staff will attempt to reach all members in arm 1, regardless of whether a telephone number is available within the Horizon member files. Therefore, Magellan staff will contact the pharmacy and/or provider office to obtain phone numbers on all members. Therefore the number of attempts made to engage a member is fewer than in other arms.

ARM 2: Adherence Risk-Targeted Moderate Intensity Intervention

Patients will receive an adherence and glycemic control outreach delivered by Magellan clinical staff. Only members with a telephone number available in the Horizon member files will be assigned to the moderate intensity intervention. Patients will be contacted by telephone and during these calls, in addition to the topics discussed in arm 1, the Magellan staff will:

4. Assess the adequacy of the patient's regimen. Staff will not suggest any changes to the patient's regimen but instead educate and encourage patient to communicate to provider.

5. Guide member-specific discussion focused on identifying potential barriers to glycemic control including availability of glucose monitoring equipment, side effects, barriers to diet and lifestyle recommendations, and education

6. Conduct motivational interviewing and educational reinforcement regarding disease state, importance of adherence, and strategies for success/improvement

In addition to the pharmacist intervention described in arm 1, this arm will include:

- Up to 6 calls total by Magellan clinical staff. If 6 calls are not deemed necessary by patient and pharmacist, the pharmacist will at the very least try to provide follow-up at 3, 6, and 9 months after randomization, where appropriate.

- One outreach call to provider or pharmacist, as needed, to update clinical status and resolve potential barrier to adherence

- Referral to a moderate intensity text messaging (TM) service as needed. The content of the TMs have been created by the BWH investigators and the TMs themselves will be delivered by the investigators to a Magellan subcontractor, Mobile Commons, which provides a service for patients to provide their cell phone numbers to receive weekly text messages in a way that is confidential. Patients will be asked to opt in.

- Quarterly follow-up letters at 3, 6, and 9 months that include information about importance of glycemic control and adherence. The schedule of mailings is listed in the table below and copies of the actual mailings are attached.

Table: Mailings schedule

Month	Arm 1	Arms 2 and 3	
0	Intro letter and postcard + pillbox	Intro letter and postcard + pillbox	Intro letter and postcard + pillbox
		Previously reached by Magellan pharmacist	Previously not reached by Magellan pharmacist
3		• Follow-up letter: previously reached member • Handout: “Understanding my insulin treatment”	• Follow-up letter: previously not reached member • Handout: “Understanding my insulin treatment”
6		• Follow-up letter: previously reached member • Handout: “Remembering to take my medicines”	• Follow-up letter: previously not reached member • Handout: “Remembering to take my medicines”
9		• Follow-up letter: previously reached member • Handout: “Maintaining my treatment plan”	• Follow-up letter: previously not reached member • Handout: “Maintaining my treatment plan”

ARM 3: Adherence Risk and Glycemic Control-Targeted High Intensity Intervention

Patients will receive the same adherence and glycemic control outreach delivered by Magellan clinical staff as described in Arm 2. Only members with a telephone number available in the Horizon member files will be assigned to the high intensity intervention.

In addition to the pharmacist interventions described in arm 2, this arm will include the following changes:

- Up to 12 calls total by Magellan clinical staff, instead of 6 calls total.

- Up to 12 outreach calls to provider or pharmacist, as needed, to update clinical status and resolve potential barrier to adherence, instead of 1 outreach call. In this scenario, the pharmacist may

discuss potential insulin dose titration with prescribing physician and communicate these changes back to the patient with the provider's permission.

- Referral to a high intensity text messaging (TM) service as needed, instead of referral to only a moderate TM service. The moderate intensity TM service includes weekly texts whereas the high intensity TM service includes daily texts. Patients will have the option to enroll in either frequency, if interested. If the patient elects into receiving daily texts, they will have the option of switching into weekly texts or no texts at any point during the intervention.

STUDY POPULATION

Patients who are potentially eligible for inclusion will be identified from the cohort of patients currently receiving health insurance from Horizon. In order to maintain generalizability, exclusion criteria will be minimal. Patients meeting the following inclusion/exclusion criteria will be selected for participation:

Inclusion criteria:

f) Commercially-insured individuals who receive medical and pharmacy health insurance benefits administered by Horizon Blue Shield Blue Cross of New Jersey
g) Age ≥ 18 years as of January 1, 2016
h) ≥ 3 months of continuous enrollment prior to randomization
i) ≥ 1 prescription for basal insulin during the 6 months prior to randomization
j) Members with type 2 diabetes, as determined by medical claims or prior prescription of an oral anti-diabetic medication (OAD)

Exclusion criteria:

b) Patients whose primary insurance is Medicaid or Medicare

Baseline HbA1c will not be an inclusion criterion. However patients with baseline HbA1c (within 6 months of randomization) will be flagged and later stratified during randomization.

RECRUITMENT PROCEDURE

Patients will be recruited into the study by a review of Horizon medical and pharmacy claims and risk scoring performed by RxAnte. After randomization, patients will be assigned to an intervention group or usual care depending on study arm, adherence risk score, and baseline HbA1c value.

All patients assigned to an intervention group will receive an introductory mailing that includes a letter introducing the pharmacist consultation and a pillbox. This letter will provide information about how to schedule a pharmacist call. In addition, patients will receive a phone call that provides the patient with an automated message explaining that they will be contacted by a pharmacist. Patient may receive up to one of

these interactive voice response (IVR) messages at the beginning of enrollment. A Magellan technician will attempt to reach the patient by phone up to 3 times in arm 1 and up to 4 times in arms 2 and 3. For patients who are not reached by phone, the Magellan team will reach out to the physician office or pharmacy to confirm current contact information.

Once a patient is reached, the Magellan pharmacist will explain the purpose of the consultation and ask the patient if he/she would like to participate. If a patient agrees, this will be considered implicit consent. If a patient wishes to not participate and wishes to not receive further contact, this will be noted and the patient will not be contacted again.

If a patient is not reached by phone with the above strategies, the patient will receive the quarterly mailing as outlined for arms 2 and 3. Data on all patients will be analyzed according to whichever group the patient was randomized to, regardless of whether the patient was reached or agreed to participate.

RANDOMIZATION

There are multiple partners who are working together to identify eligible patients and deliver the intervention. Our goal is to use the minimal amount of clinical data necessary at each step in order to implement the intervention. Because of the large number of patients who will be contacted by Magellan pharmacists, patient selection, randomization, and recruitment will occur over the first 4 months of the trial. This will require the following steps:

- Horizon analytics team will send claims data on all insulin users from 2013 to 2015 to RxAnte to perform validation of insulin adherence risk scores. Before the study starts, Horizon will send updated enrollment files.
- RxAnte will assign risk scores on all insulin users and send risk scores to Horizon
- Horizon will apply inclusion and exclusion criteria and select patients eligible for randomization. They will flag patients with baseline HbA1c values, claims-based diabetes diagnosis (in contrast to OAD-based diabetes diagnosis, and telephone number availability).
- Horizon will randomize 1,500 patients meeting criteria above. Randomization will be stratified by HbA1c availability, claims-based diabetes diagnosis, and telephone number availability.
- Horizon will send the following aggregated and de-identified data to Brigham: distribution of risk scores and HbA1c values in arms 2 and 3. Brigham investigators will choose risk score and HbA1c cut-offs that will result in appropriate targeting levels.
- Brigham will send these cut-offs to Horizon. The Horizon analytics team will apply these thresholds to make intervention assignments within each randomized group.
- Horizon will send the necessary data on all patients assigned to receive an intervention to Magellan.
- The process above will be repeated monthly 3 additional times so that randomized and recruitment is staggered over the course of 4 months.

Randomization will occur in a 1:1:1 ratio conducted on the patient level. In order to have adequate power to study our secondary outcome, change in HbA1c, our randomization will be stratified on patients with baseline HbA1c lab availability within the 6 months prior to randomization.

This randomization will occur using a random number generator at Horizon Analytics. Randomization codes will be assigned strictly sequentially as patients become eligible. The randomization key will be maintained at Horizon Analytics as well as the allocation of patients to the intervention arms.

Data Sources

The data that will be used for patient selection and analysis includes medical and pharmacy claims and lab data from Horizon. Complete paid pharmacy and medical services claims data will be combined into a database consisting of all filled prescription, procedures, inpatient and outpatient physician encounters, hospitalizations, long-term care admissions and deaths for all patients studied.

In addition to the Horizon claims data, both vendors will provide de-identified aggregate data on risk prediction and patient contact to Brigham investigators. Specifically, RxAnte will provide aggregate risk prediction scores from their initial scoring. These scores will be linked to an anonymous patient ID (the link between patient ID and medical record number will be kept by Horizon analytics). Magellan will provide a monthly report of how many patients were reached and the type of contact (e.g. number of patients who were engaged on the telephone, the number of providers who were contacted).

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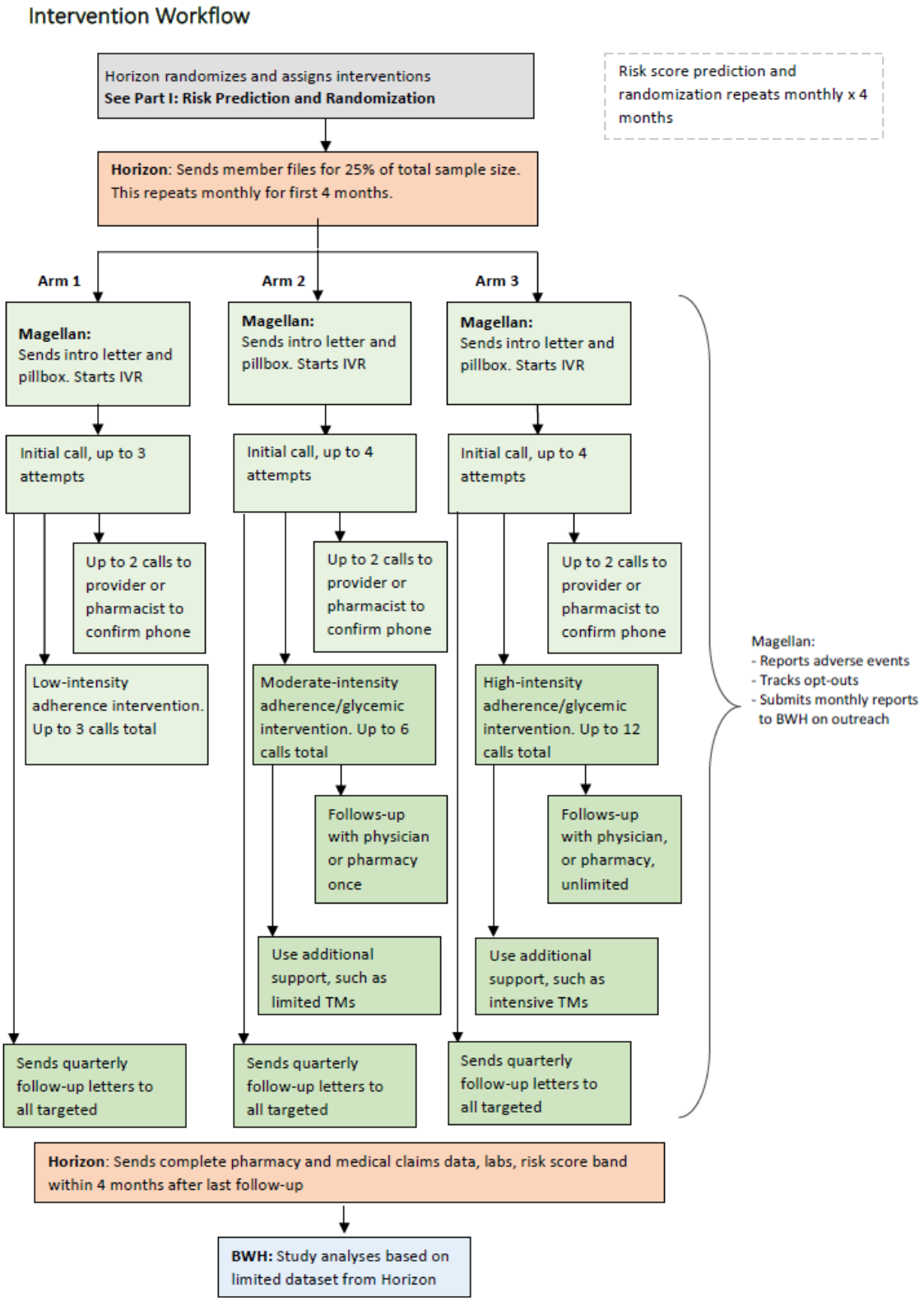
Appendix B: Study Workflow



Summary of changes to protocol

Date of submission	Description of modification	Rationale for modification	Approval date
Original IRB submission	-	-	4/29/2016
8/22/2016	Small adjustments were made in terms of how to assign patients to specific interventions in each arm based upon whether the patient had an available phone number or not.	We received pilot data from Horizon about the proportion of eligible subjects with missing telephone numbers to adjust the intervention deployment,	9/12/2016

OUTCOME MEASURES

Primary outcome: insulin persistence at 12 months

Insulin persistence: this is a binary outcome that labels the patient as persistent or non-persistent to insulin at 12 months. The patient will be categorized as being persistent if a refill is observed within the expected time of medication coverage for stratum of metric quantity dispensed, defined as the 90th percentile of time, between the first and second fills among patients with at least one refill. The 90th percentile of time will be determined based on the model building cohort using historical Horizon data and will be measured using Horizon pharmacy claims.

Secondary outcomes

Mean change in HbA1c: change in HbA1c from baseline to follow-up, averaged over the study arm. HbA1c values obtained 6-12 months after randomization will be used for follow-up. If multiple HbA1c values are present, the value closest to 12 months will be used. HbA1c values will be assessed using lab data provided to Horizon.

Health care spending: This will be calculated from allowed amounts appearing in Horizon's claims data for prescription medications, nondrug medical services, and the combination of these two factors after the assignment of the patient to a study group.

Rates of healthcare utilization: Rates of medical follow-up including physician visits, emergency room visits, hospitalization will be calculated based on Horizon's claims data for nondrug medical services.

Alternative measures of insulin persistence: these measures include defining persistence as having a gap between insulin prescriptions < 90 days and refilling within 30 or 60 days of after date of previous fill plus days supply.

Statistical analyses

All analyses will be performed based on intention-to-treat principles. Rates of insulin persistence and time to non-persistence will be compared using Kaplan-Meier estimates and Cox proportional hazards models. If there are differences in baseline characteristics between study groups that are believed to be confounders of the intervention–outcome association, we will repeat our analyses after adjusting for these covariates. Patients will be censored at time of non-persistence, loss of insurance eligibility, or end of follow-up, whichever occurs first. Mean change in HbA1c will be compared using Student's t-test or Wilcoxon rank sum test. Analysis of healthcare utilization and healthcare cost will be performed using generalized estimating equations. An additional per protocol analysis will be conducted to compare rates of insulin persistence and mean change in HbA1c among patients intervened upon.

Sample size calculation

Based on prior work by Wei et al.[12], the proportion of patients persistent to insulin after 12 months in a commercially insured population is 65%. Assuming that 40% of targeted individuals are reached by

Magellan in each of the three arms and that less than 10% of subjects are lost to follow-up, randomizing 2,000 patients into each arm would give us more than 80% power at an alpha threshold of 0.05 to detect at least a 9% increase in the proportion of patients who are persistent with insulin between study arms 2 and 1 and at least an 11% increase between study arms 3 and 1. We believe this is a clinically meaningful difference and is feasible given the sample size estimates we calculated with the assistance of the Horizon analytics team using their 2014 enrollment data. Under these same assumptions but assuming a reach rate of 30% by Magellan, we would have 80% power at an alpha threshold of 0.05 to detect an 11% increase in the proportion of patients who are persistent with insulin between study arms 2 and 1 and a 13% increase between arms 3 and 1.

OUTCOME MEASURES

Primary outcome: insulin persistence at 12 months

Insulin persistence: this is a binary outcome that labels the patient as persistent or non-persistent to insulin at 12 months. The patient will be categorized as being persistent if a refill is observed within the expected time of medication coverage for stratum of metric quantity dispensed, defined as the 90th percentile of time, between the first and second fills among patients with at least one refill. The 90th percentile of time will be determined based on the model building cohort using historical Horizon data and will be measured using Horizon pharmacy claims. This threshold is formally defined as the 90th percentile of the time between the first insulin fill after follow-up and the second insulin fill, adjusting for insulin type and quantity dispensed. For example, 90% of Horizon members refilled their prescription for insulin glargine (15 units) within 141 days of their first prescription in 2012-2015. We will prospectively apply this 90th percentile cut-off based on historical data to patients in this study. This process will be repeated to define 90th percentile thresholds for the time between the second and third refill, the third and fourth refill and so on, and patients will be considered non-persistent if they fail to refill before any of these threshold times has elapsed.

Patients will be considered persistent if they fill a prescription for the same or a different basal insulin. If the patient switches basal insulins, we will apply the appropriate threshold for the 90th percentile of time. Patients who have 1 or fewer insulin fills (i.e. no "refills") during follow-up will be considered non-persistent on the day of the 90th percentile threshold. Patients who are censored before their 90th percentile non-persistence threshold date will be considered persistent.

Secondary outcomes

Mean change in HbA1c: Glycemic control will be measured as mean change in HbA1c from baseline to follow-up among those patients with baseline HbA1c available. Because clinical data will not be explicitly collected as part of this pragmatic study, laboratory values will be assessed using data provided to Horizon as part of routine quality monitoring. The HbA1c result recorded closest to the 12-month end of follow-up, up to 15 months after randomization, will be used in the analysis. We will impute missing follow-up HbA1c values for those patients with an available baseline result availability but a missing follow-up result using multiple imputation. Changes in HbA1c without imputed values will also be reported as a sensitivity analysis.

Health care spending: This will be calculated from allowed amounts appearing in Horizon's claims data for prescription medications, nondrug medical services, and the combination of these two factors after the assignment of the patient to a study group.

Rates of healthcare utilization: Rates of medical follow-up including physician visits, emergency room visits, hospitalization will be calculated based on Horizon's claims data for nondrug medical services.

Statistical analyses

All analyses will be performed based on intention-to-treat principles.

Because of the time required for data processing and transfers, follow-up measurements will begin 1 month after randomization, which is the earliest time patients could receive the intervention.

In the primary analysis, the relative risk of insulin non-persistence between treatment arms will be compared for each insulin fill in the follow-up period using modified Poisson regression with robust error variance. For this analysis, we will use generalized estimating equations with a log link function, Poisson-distributed errors, and account for correlations in the repeated measurements among patients over time. The primary models will adjust for the stratified randomized design. If there are differences in baseline characteristics between study groups that are believed to be confounders of the intervention–outcome association, we will repeat our analyses after adjusting for these covariates. Patients will be censored at time of non-persistence, loss of insurance eligibility, or end of follow-up, whichever occurs first.

We will conduct a subgroup analysis among patients with at least 2 insulin fills after the follow-up period begins. Sensitivity analyses will include applying alternative methods of measuring insulin use as defined in the literature, such as gap-based measures and medication possession ratio based on days of insulin supplied in each prescription. Rates of insulin persistence and time to non-persistence will be compared using Cox proportional hazards models in secondary analyses. If there are differences in baseline characteristics between study groups that are believed to be confounders of the intervention–outcome association, we will repeat our analyses after adjusting for these covariates. Subgroup analyses will be conducted to assess whether the impact of the intervention varies according to key patient characteristics.

Change in mean HbA1c will be analyzed using generalized estimating equations with an identity link function and normally distributed errors, also adjusting for the stratification of randomization. Analysis of healthcare utilization and healthcare cost will be performed using generalized estimating equations using a log link with Poisson distributed errors.

Sample size calculation

Based on prior work by Wei et al.[12], the proportion of patients persistent to insulin after 12 months in a commercially insured population is 65%. Assuming that 40% of targeted individuals are reached by Magellan in each of the three arms and that less than 10% of subjects are lost to follow-up, randomizing 2,000 patients into each arm would give us more than 80% power at an alpha threshold of 0.05 to detect at least a 9% increase in the proportion of patients who are persistent with insulin between study arms 2 and 1 and at least an 11% increase between study arms 3 and 1. We believe this is a clinically meaningful difference and is feasible given the sample size estimates we calculated with the assistance of the Horizon analytics team using their 2014 enrollment data. Under these same assumptions but assuming a reach rate of 30% by Magellan, we would have 80% power at an alpha threshold of 0.05 to detect an 11% increase in the proportion of patients who are persistent with insulin between study arms 2 and 1 and a 13% increase between arms 3 and 1.

Summary of changes to the analysis plan

The primary and secondary outcomes are now further clarified along with the specific analytic strategy for these outcomes.