Targeted Adherence Intervention to Reach Glycemic Control with Insulin Therapy for patients with Diabetes (TARGIT-Diabetes): rationale and design of a pragmatic randomised clinical trial

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Introduction
Adherence to and persistence of medications for chronic diseases remains poor and many interventions to improve medication use have only been modestly effective. Targeting interventions to patients who are most likely to benefit should improve their efficiency and clinical impact. This study aims to test the impact of three cost-equivalent pharmacist-led interventions on insulin persistence and glycaemic control among patients with diabetes.

Methods and analysis
TARGIT-Diabetes (Targeted Adherence Intervention to Reach Glycemic Control with Insulin Therapy for patients with Diabetes) is a randomised controlled trial that will evaluate three different multifaceted pharmacist-outreach strategies for improving long-term insulin use among individuals with diabetes. We will randomise 6000 patients in a large insurer to one of three arms. The arms are designed to deliver an increasingly intensive intervention to a progressively targeted population, identified using predictive analytics. The central component of the intervention in all arms is a tailored telephone consultation with a pharmacist which varies across arms based on the: (A) proportion of patients offered the intervention and (B) intervention intensity, including follow-up frequency and cointerventions such as text reminders and interactions with patients’ providers. The primary outcome is insulin persistence, assessed using pharmacy claims data, and the secondary outcomes are glycaemic control as measured by glycosylated haemoglobin values, healthcare utilisation and healthcare spending.

Ethics and dissemination
This protocol has been approved by the Institutional Review Board of Brigham and Women’s Hospital and the Privacy Board of Horizon Blue Cross Blue Shield of New Jersey. We plan to present the results of this trial at national meetings and in manuscripts submitted to peer-reviewed journals.

Trial registration number
NCT 02846779.

Background
Adherence to chronic disease medications remains poor and decreases over time, with almost half of all patients becoming non-adherent within 6 months of starting a new medication. Medication non-adherence, which includes skipping doses, and non-persistence, the early and inappropriate discontinuation of medication, are risk factors for adverse clinical outcomes, including hospital admissions, and cost the US healthcare system over $100 billion annually. Barriers to appropriate medication use are complex, yet interventions designed to improve adherence
and persistence are often simple and broadly delivered.6–8 As a result, the clinical impact of even multifaceted interventions has been modest.89

Improving the use of evidence-based therapies will not likely occur with a ‘one size fits all’ approach. Effectively targeting the right intervention to patients who are most likely to benefit should improve the impact and efficiency of interventions designed to improve long-term medication use and is an area of particular relevance in the era of healthcare cost containment.10 11 For example, medically complex patients, such as those with uncontrolled chronic conditions or those who are less likely to take medications as prescribed, may require higher intensity interventions to improve long-term medication use and disease control, whereas patients with unintentional non-persistence due to forgetfulness or carelessness may respond to simple interventions, such as reminders.12 13 Further targeting patients with poor disease control may potentiate the impact of any outreach.14

One particular group at high risk for the consequences of non-persistence are individuals with diabetes treated with insulin.15 In addition to the frequently reported barriers that exist for oral hypoglycaemics, there are unique challenges to the consistent use of insulin including anxiety about performing self-injection, fear of hypoglycaemia and a lack of confidence in the efficacy of the medication.16–19 Safely administering insulin and monitoring the response may impose significant lifestyle changes for some patients.15 Accordingly, rates of insulin discontinuation are high.20 21 Despite this, few insulin-requiring patients have historically been included in intervention trials in part because of the difficulty of measuring persistence using routinely collected data.22

TARGIT-Diabetes (Targeted Adherence Intervention to Reach Glycemic Control with Insulin Therapy for patients with Diabetes) is a randomised controlled trial that seeks to improve insulin persistence and glycaemic control and identify whether increasing the focus and intensity of an intervention on a smaller number of high-risk patients is more effective than deploying less intervention to a greater number of patients.

OVERALL STUDY DESIGN
TARGIT-Diabetes is a pragmatic, prospective, three-arm randomised controlled trial designed to evaluate different pharmacist-outreach strategies for improving persistence to basal insulin among individuals with diabetes. The trial is funded by Sanofi US and is registered in ClinicalTrials.gov (NCT 02846779). Data collection began in July 2016 and will be completed by November 2017.

STUDY SETTINGS AND SUBJECTS
We will enroll individuals whose medical and prescription benefits are administered by Horizon Blue Cross Blue Shield of New Jersey (Horizon), the largest health insurer in New Jersey with over 3.8 million beneficiaries. Potentially eligible patients will be at least 18 years of age and who have a diagnosis of type 2 diabetes, as assessed by administrative claims or prior fill of an oral antidiabetic medication, who filled at least one prescription for basal insulin during the 6 months prior to randomisation, including detemir, glargine, lispro protamine and NPH formulations (see online supplementary appendix table 1 for full list). Patients who are insured by Medicaid or Medicare and those who do not have at least 3 months of continuous insurance enrolment immediately prior to randomisation are ineligible for inclusion.

INTERVENTIONS AND STUDY PROCEDURES
The core element of the multifaceted intervention in each of the three study arms is an individually tailored telephone consultation conducted by a clinical pharmacist. The nature of the outreach and strategies and solutions offered during the consultation is similar across the three arms; however, the arms differ in the number of patients who receive the intervention (see figure 1) and the frequency of follow-up and availability of complementary engagement methods (see table 1). The three intervention approaches were designed to be equivalently priced in order to simulate the choice that a health insurer or health system would make in allocating funds to improve the quality of care and outcomes for a given population of patients. The costs were determined by Magellan Rx Management, a pharmacy benefit management company that provides healthcare management services and were based on the estimated time for personnel involvement for pharmacists and support staff, mailings, text messaging and clinical oversight. In order to maintain equivalent pricing across the three study arms, the proportion of patients targeted in arms 2 and 3 (60% and 40%, respectively) is balanced against the increasing cost of more intensive outreach and follow-up.

Arm 1: non-targeted low-intensity intervention
This treatment arm is designed to mimic the standard of care that might be delivered by an insurer to its beneficiaries as part of quality improvement outreach. All patients assigned to this treatment arm are sent a letter informing them about the pharmacist outreach, a reminder postcard, and a simple, two-compartment per day pillbox that allows for the storage of 1 week of medication. The postcard serves as a primer for the patient to think about their diabetes medications and barriers to good adherence. Pharmacists then attempt to reach everyone assigned to this treatment arm. Prior to pharmacist consultation, each patient will receive an interactive voice recognition (IVR) call to alert them that a pharmacist will be calling them.

The consultations are provided by pharmacists at Magellan Rx Management. Prior to study launch, all pharmacists received training in medication therapy management and motivational interviewing by internal staff. Motivational interviewing served as a framework...
Figure 1 Targeting and intervention assignment.

Table 1 Summary of intervention components

<table>
<thead>
<tr>
<th>Intervention components</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised, n</td>
<td>2000</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>Patients assigned to intervention, n</td>
<td>2000</td>
<td>1200</td>
<td>800</td>
</tr>
<tr>
<td>Introductory letter and pillbox</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quarterly educational mailings</td>
<td>None</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Max call attempts to engage patient*, n</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Max calls to engaged patient†, n</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Max calls to pharmacy/ provider for clinical follow-up, n</td>
<td>0</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Available text messaging service</td>
<td>None</td>
<td>Weekly</td>
<td>Weekly, every 3 days or daily</td>
</tr>
</tbody>
</table>

*Maximum number of calls made to reach patient for initial consultation.
†Maximum number of calls made to patients who are reached.
max, maximum.

for the intervention, which is based on principles of establishing relationships between clinician and patients and expressing empathy. The consultation is designed to: 1) confirm the patient’s current diabetes treatment regimen and their goals of therapy; 2) engage patients in a discussion about their individual beliefs and expectations of treatment and barriers to medication persistence including side effects, complexity of regimen, education, cost and expectations of treatment; and 3) provide counselling and educational reinforcement regarding good glycaemic control, the importance of long-term medication use, and strategies for ongoing success and/or improvement. Pharmacists will primarily focus on issues related to insulin use but will provide support for any other diabetic medications the patient may be taking. After the initial phone consultation, patients can receive two follow-up calls for a total of three phone calls.

Arm 2: non-persistence risk-targeted moderate-intensity intervention

In this arm, patients with a higher predicted risk of future insulin discontinuation are selected for a more intensive intervention than that received by patients assigned to arm 1. Specifically, 60% of patients are targeted for intervention based on their future
non-persistence risk. The insulin persistence risk score prediction is performed by RxAnte, whose proprietary analytics platform uses standard insurer enrolment and pharmacy and medical claims data to predict future insulin use. Patients with a moderate predicted risk of insulin non-persistence (between 10% and 90%) are targeted (‘high-value’ targeting) in order to focus on those individuals who were most likely to benefit from the intervention. As a result, patients predicted to have the highest probability of persistence, and therefore do not require support for appropriate medication use, or the lowest probability of persistence, who are likely to be the most difficult to engage via a telephone-based intervention, received usual clinical care without pharmacist intervention.

Targeted patients (those randomised to arm 2 and assigned to receive the intervention) will receive all intervention components described in the low-intensity intervention arm but can receive a total of six (as opposed to only three) phone calls, distributed over the course of 12 months. With the patient’s permission, the pharmacist can offer follow-up with the patient’s primary care provider and/or pharmacist that is limited to providing them with updates about the patient’s clinical status or resolving a potential barrier to insulin persistence, such as requesting 90-day prescription fills. Patients are also offered the opportunity to receive weekly SMS (short message service) text messages via a secure messaging platform (Mobile Commons; Brooklyn, NY) for the 12-month follow-up period or until the patient opts out. These unique text messages were developed by the study team to provide motivation for and promote engagement with study participants about medication-taking behaviour, healthy lifestyle choices and importance of good glycaemic control.

**Arm 3: non-persistence risk and glycaemic control-targeted high-intensity intervention**

In this arm, subjects are targeted for intervention based on their predicted risk of future insulin discontinuation and their glycaemic control. A smaller proportion of patients are offered a high-intensity intervention than in arm 2 (ie, 40% in arm 3 as compared with 60% in arm 2). Specifically, patients are selected for the intervention if their future probability of persistence was between 20% and 80% and their baseline haemoglobin A1c (HbA1c) was above ≥8%, the target defined by the American Diabetes Association clinical guidelines. Subjects without HbA1c values are also included because the lack of such data suggests worse disease control and a higher risk of adverse outcomes. Missing HbA1c values may be a marker of non-engagement with care and therefore indicate a high potential for benefit from an intervention such as the one we are testing. Missing HbA1c values may also occur because patients used laboratories that do not routinely send results to Horizon. Further, incomplete laboratory availability represents the clinical reality of many insurers and therefore we sought to test an intervention in a way that would maximise the generalisability of our results.

Patients assigned to this group will receive all outreach components described in the low and moderate-intensity intervention groups but in addition will be able to receive a total of 12 phone calls. The pharmacist can follow-up with the patient’s diabetes provider and/or pharmacists as many times as needed to discuss and address any clinical scenario without restriction. Such outreach may include the communication of poorly controlled home glucose measurements and side effects which may lead to insulin dose changes or regimen changes. Patients will also have the opportunity to enroll in an SMS text messaging programme but can choose whether to receive messages weekly, every 3 days or daily. This intervention is designed to represent the most intensive type of patient engagement strategy that a telephone-based disease management programme can offer.

**RANDOMISATION**

Study enrolment began in July 2016 and was completed by 13 October 2016. Eligible subjects will be randomised in a 1:1:1 ratio to one of three treatment arms using a random number generator by a data analyst at Horizon. Slightly more than half of patients (54%) have a recent HbA1c result documented in the Horizon data and randomisation will be stratified based on lab result availability. We will randomise 1500 patients monthly over 4 months for a total sample size of 6000 patients. Patient eligibility and persistence risk prediction will be assessed a total of four times. Given constraints on how many pharmacist calls could be made in any month, we will stagger randomisation over 4 months in order to minimise the amount of time between randomisation and initial outreach. As described above, after randomisation, patients will be assigned to the moderate or high-intensity intervention or usual care based on their HbA1c values and/or persistence risk score. Intervention assignment will be performed by study investigators at Brigham and Women’s Hospital.

**OUTCOMES**

Non-persistence will be measured using the persistence assessment method proposed by Wei et al. With this approach, prescription claims data are used to classify patients as non-persistent if they do not have an insulin refill before a set threshold of time. This threshold is assigned based on historical data from Horizon and 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 (see online supplementary appendix figure 1). 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 refills, the third and fourth refills, and so on, and patients will be considered non-persistent if they fail to refill before any of these threshold times have 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.

Because of the time required for data processing and transfers, follow-up measurements will begin 1 month after randomisation, which is the earliest time patients could receive the intervention. Patients will be censored at the end of study follow-up (12 months after randomisation) or disenrolment from Horizon insurance. Patients who have one or fewer insulin fills (ie, 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. We will conduct a subgroup analysis among patients with at least two 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 measures29 and medication possession ratio based on days of insulin supplied in each prescription.29

The secondary outcomes are glycaemic control, total healthcare utilisation and healthcare spending. Glycaemic 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 randomisation, will be used in the analysis.30 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. Multiple imputation is used to generate multiple results for missing values from the underlying distribution of the available data and allows an analysis of multiple and combined results.31-33 Changes in HbA1c without imputed values will also be reported as a sensitivity analysis. Rates of healthcare utilisation will be measured using administrative claims data and will include all-cause emergency room visits, physician visits and hospitalisations during follow-up, as well as care related to hypoglycaemia. Healthcare spending will be assessed from the total allowed amount for medical and pharmacy claims from the administrative claims. A full set of primary and secondary outcomes is described in box. Subgroup analyses will be conducted to assess whether the impact of the intervention varies according to key patient characteristics.

**Box Primary and secondary outcomes**

**Primary outcome: insulin persistence**
Fills insulin within expected time of medication coverage from beginning of follow-up through end of study

**Secondary outcomes**
- Change in HbA1c among patients with baseline HbA1c availability
- Healthcare spending
- Healthcare utilisation (outpatient visits, emergency room visits, hospitalisations)

**Analytical plan**
All analyses will compare all patients in the moderate and high-intensity intervention arms separately from the low-intensity treatment arm, which is considered the standard of care. We will include all patients randomised in the study in these analyses. We will describe the reach rates and number of pharmacist contacts in each arm. We will also descriptively examine the number of follow-up calls and the number of patients who self-reported poor adherence to insulin. We will report the means and frequencies of prerandomisation variables, including demographics, baseline medication use and coexisting illnesses, separately for the three intervention arms. We will also report follow-up insulin persistence and glycaemic control for the 60% and 40% of patients assigned to the intervention in arms 2 and 3 in addition to arms 2 and 3 overall.

Comparisons of these values for the moderate and high-intensity intervention to the low-intensity arm will be performed using t-tests and \(X^2\) tests and their non-parametric analogues, as appropriate. The outcomes will be evaluated using intention-to-treat principles among all randomised patients. 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 generalised estimating equations with a log link function, Poisson-distributed errors and account for correlations in the repeated measurements among patients over time.34 The primary models will adjust for the stratified randomised 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. In secondary analyses, we will use a time-to-event approach and Cox proportional hazards model to evaluate the hazard of discontinuing overall insulin therapy over the follow-up period.

Change in mean HbA1c will be analysed using generalised estimating equations with an identity link function and normally distributed errors, also adjusting for the stratification of randomisation. Analysis of healthcare utilisation and healthcare cost will be performed using generalised estimating equations using a log link with Poisson-distributed errors.
SAMPLE SIZE CONSIDERATIONS

We powered the study to detect a clinically meaningful 15% relative decrease in the risk of insulin non-persistence between study arm 2 or 3 and arm 1 (ie, a risk ratio of 1.15) which is equivalent to approximately 200 fewer patients becoming non-adherent in our targeted groups in arms 2 and 3 compared with arm 1. We estimated that we would have 80% power at an alpha threshold of 0.05 to detect this effect by randomising 2000 patients to each arm, assuming that the risk of non-persistence to insulin after 12 months in a commercially insured population is 35%. 24

LIMITATIONS

The primary outcome in this trial is insulin persistence and not the extent to which a patient has experienced clinical improvement. Measuring insulin persistence presents unique challenges given that it is an injectable medicine with potentially variable dosing within and among patients. There may be misclassification of persistence in the setting of significant dosing changes or large prescription amounts. Persistence measures may not be accurate for patients who refill insulin prescriptions at regular intervals despite not taking it (stockpiling) or pay out of pocket without using insurance benefits.

Diabetes control will also be assessed as a secondary outcome by change in HbA1c, but our evaluation will be limited to those patients for whom Horizon has baseline laboratory availability and we may be underpowered to detect even a moderate change in glycaemic control. The lack of complete clinical data is a common challenge for health insurers and health systems implementing quality improvement interventions. Nonetheless, higher levels of insulin persistence are associated with improvement in clinical outcomes and are consistent with quality measures that use medication adherence as an intermediate outcome, such as the Centers for Medicare and Medicaid Services Star Ratings measures. 24 35

We are targeting patients for a high-intensity intervention in arm 3 based on predicted risk of insulin discontinuation as well as poor or missing HbA1c values. Missing HbA1c values may be a marker of low engagement and poor disease control. This approach may also identify patients who use non-Horizon-affiliated laboratories regardless of disease control. As such, we may intervene on patients in arm 3 who have good disease control but a high predicted risk of non-persistence. These patients may not benefit as much from the intervention and this may conservatively bias our results towards the null.

We will use multiple methods to engage patients. All patients assigned to receive an intervention will receive IVR calls prior to the first pharmacist call, a small incentive (specifically, a pillbox), a postcard designed to prime the patient for the pharmacist call and serve as a commitment device, and repeated phone call attempts by the pharmacist with follow-up with provider’s office and/or pharmacy for non-working numbers. Nevertheless, our study may be underpowered if our engagement rates are significantly lower than 40%.

We will have progressive degrees of patient targeting in the moderate and high-intensity intervention arms of the study that depend on the analysis of large amounts of historical administrative data to predict the risk of medication non-persistence. The results may not be fully generalisable to health systems not currently utilising such platforms. Although we are utilising a proprietary algorithm for risk prediction in this study, given the increasing trends towards risk prediction in population health management programmes, we anticipate that many health systems will be developing internal capacity or external vendor relationships in the future.

We designed the study with three active comparison groups to mimic the real-world trend of providing some degree of quality improvement outreach to members with diabetes. Without a true control group, we are unable to test for differences between the low-intensity intervention and no intervention at all.

CONCLUSION

TARGIT-Diabetes is a pragmatic randomised controlled trial that will determine the best method of patient targeting and deploying quality improvement strategies to high-risk patients with diabetes in order to improve insulin persistence and glycaemic control. The primary and secondary outcomes are measured using data generated during the routine clinical care of patients with diabetes. By embedding the clinical trial within a large health insurance system and limiting the exclusion criteria, our goal is to mimic a ‘real-world’ setting in which to compare three equivalent-priced strategies in order to aid the implementation and dissemination of the most effective strategy given a set amount of resources.

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Contributors WW, SJ and NKC conceived the study. JL, WW, JCL, SJ and NKC initiated the study design and SM, AC, JDG and GN helped with implementation. NKC is a grant holder. All authors contributed to refinement of the study protocol and approved the final manuscript.

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