# CLINICAL TRIAL PROTOCOL

**Reinforcement learning to personalize message framing for healthy habits (REINFORCE)**

**National Clinical Trial (NCT) Identified Number: NCT04473326**

---

**Principal Investigators:**
Julie C. Lauffenburger, PharmD, PhD
Niteesh K. Choudhry, MD, PhD

Center for Healthcare Delivery Sciences and Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School

Funded by the National Institute on Aging
Grant Number: P30AG064199

Version: No. 4, April 1, 2021

**Detailed Protocol – Reinforcement Learning in Diabetes Mellitus Trial**
PI: Lauffenburger
Version 5. April 1 2021

**Background and Significance**

Highly influential in motivating behavior change is the prominence of information or how information is framed. For example, providing information to patients in terms of risks rather than benefits makes them two times more willing to fill a prescribed medication. A potential way to optimize behavior is through problem solving, specifically trial and error. While manual trial and error is infeasible at scale, reinforcement learning offers a path forward. In specific, reinforcement learning is an advanced analytic method that discovers each individual's pattern of responsiveness by observing their actions and then implements a personalized strategy to optimize individuals' behaviors using trial and error. This method was developed based on principles of behavioral science to help models make better decisions based on human behavior. In contrast to other approaches that use previously-collected data, reinforcement learning algorithms learn in real-time and can personalize for specific patients. Given its theoretical foundation and ability to adapt in real-time, reinforcement learning holds wide promise for changing – and sustaining – health behaviors.

The goal of the proposed study is to develop and test a novel reinforcement learning-enhanced text messaging program to support medication adherence in patients with type 2 diabetes. Type 2 diabetes is an optimal condition in which to test this program, as it is one of the most prevalent chronic conditions in the US adult population and requires most patients to be on daily or twice daily doses of medications.

**Specific Aims**

This pilot seeks to utilize two principle-driven interventions, message framing and reinforcement learning, to motivate adherence to evidence-based medications for adults with type 2 diabetes. To accomplish this aim, this project consists of two phases. **This present protocol focuses only on the second phase, which is a small pragmatic trial.**

This phase has the following aims:

(A) *To determine whether a novel reinforcement-learning text messaging program improves adherence to medications and clinical outcomes.* We will conduct a small pragmatic trial to determine the feasibility and efficacy of using reinforcement learning on patient adherence to diabetes medications.

(B) *To classify patient responsiveness to reinforcement learning.* We will cluster intervention patients by their response to different types of messages (e.g., negative or positive framing) and evaluate the ability to predict these cluster phenotypes using information prior to randomization. This approach will optimize the design of future interventions by eliminating the need for electronic pill monitoring to determine clusters.

**Subject Selection**

Phase 2: Pragmatic Trial

- We will enroll and randomize 60 eligible male and female patients (30 each to intervention and usual care arms) receiving their care at a BWH-affiliated diabetes practice who are between 18-84 years of age with type 2 diabetes mellitus (T2DM) and are prescribed between 1-3 daily oral medications for this disease. Patients must have a smartphone with a

data plan or WiFi at home, an HbA1c level ≥7.5%, basic working knowledge of English, no active enrollment in another diabetes trial within Mass General Brigham, and ability to set up the platform and adhere to study procedures. To be included, patients must also either not currently use a pillbox or be willing to use electronic pill bottles (EDMs) for their diabetes medications for the duration of the study. This criterion is primarily because if patients were to concomitantly use pillboxes for these medications, it would undermine our ability to measure their adherence patterns.

- Patients will be enrolled in an experimental study that involves a Pillsy electronic pill bottle. These electronic pill bottles have been used by other research studies at MGB. While the Pillsy bottle offers a set of "smart" functionalities, we will only use the bottle as a container for oral medication and as a measurement of adherence. Participants will be asked to use the Pillsy bottle for 6 months. Throughout the 6-month study period, the electronic pill bottles will record daily medication use.
- Patients in the intervention arm will receive up to daily text messages based on their EDM-measured adherence. Based on patient's baseline characteristics and time-varying responses to the messages, a reinforcement learning algorithm will determine which type of messaging works best for each individual patient. A text messaging platform will deliver different text messages and adapt over time to the messages that individual patients most respond to.
- Patients in the usual care arm may receive up to daily, untailored messages.
- At the end of the study period, participants' medication adherence and diabetes-related outcomes will be evaluated.

At this time, we are requesting IRB approval for the trial portion of our study (Phase 2, described above).

**Subject Enrollment**

- Patients for the study will be recruited from the Brigham and Women's Hospital outpatient diabetes clinics at 221 Longwood Ave, 45 Francis Street, and Brigham and Women's Faulkner Hospital.
- Patients will be recruited weekly through two mechanisms used in prior studies:
    - First, we will ask endocrinologists to refer potentially eligible patients since a similar referral system has been successful for several studies in the department. We will include all patients receiving care at a BWH-affiliated endocrinology practice. We will ask them to introduce the study to their patients with a fact sheet. (See Attachments).
    - Second, we will use both a weekly EPIC screen for patients with upcoming appointments and RPDR to identify patients with type 2 diabetes who are receiving care from a BWH endocrinologist, and who are taking 1-3 oral medications for their disease. We will reach out to the identified patients' endocrinologist to ask them to opt out the patient if they do not consider them appropriate for the study. We will include a Fact Sheet for them to understand the study and its procedures. If within a week the provider does not opt out of the study for their patient, we will send a letter to the patient on their behalf inviting them to participate. We will then

contact the patient over the phone a week later to inquire about participation. (See Attachments).

- Patient Gateway will also be used intermittently throughout the recruitment period to identify potentially eligible patients who have an assigned endocrinologist at one of these BWH outpatient diabetes clinics. In specific, following the same process as outlined above, we will reach out to the identified patients' endocrinologist to ask them to opt out the patient if they do not consider them appropriate for the study. We will include the Fact Sheet for them to understand the study and its procedures. If within a week the provider does not opt out of the study for their patient, we will send a letter via Patient Gateway to the patient on their behalf inviting them to participate. We will then contact the patient over the phone a week later to inquire about participation. (See Attachments).

During the patient's clinic visit (virtual or in-person), a research assistant will screen the patient for eligibility and obtain consent from the participant to participate in the study. **All procedures for this study can be done completely virtually.**

Patients will be screened for eligibility using a screening form (See Attachments). This form will be completed directly in REDCap for all patients screened. Patients will consent to participate in the study by signing the Written Consent form (see Attachments). If this visit is completed virtually via one of MGB's approved video platforms (e.g., Zoom), the study staff will be virtually present for the consent process and will obtain electronic informed consent from the participant using MGB-approved REDCap e-consent/paperless consent process.

We will include the below text in secure emails or via Partners Patient Gateway, so that patients will have the ability to opt-out:

"The Mass General Brigham (MGB) standard is to send email securely. This requires you to initially set up and activate an account with a password. You can then use the password to access secure emails sent to you from MGB. If you prefer, we can send you "unencrypted" email that is not secure and could result in the unauthorized use or disclosure of your information. If you want to receive communications by unencrypted email despite these risks, MGB will not be held responsible. Your preference to receive unencrypted email will apply to:

> for research: [emails sent to you from research staff in this study. If you wish to communicate with other research staff at MGB regarding additional studies, your preference will have to be documented with each research group.]
>
> for clinicians: [emails sent from clinicians and staff at this practice or department.]
>
> for finance: [emails sent to you from Patient Billing Solutions and the Patient Service Center."]

Please confirm receipt of this email and indicate if your preference is to NOT receive secure emails from me at this time. If I do not hear back from you, then all future emails will be sent either via patient gateway or via secure messaging as is MGB policy."

Patients who prefer to correspond via email and to complete surveys electronically, will have the option to do so securely via the above channels for email and via REDCap, with all links sent securely as well.

**Study Procedures**

Participants have two study-related visits. These study visits can be completed virtually or in-person during clinic visits (if/when COVID-19 precautions are lifted) and both sets of procedures are described in further detail below.

Using a random number generator using stratification by baseline self-reported adherence and HbA1c control, the study research assistant will randomize 30 patients to the reinforcement learning arm and 30 patients to usual care. Other clinic staff and analysts will be blinded to arm assignment.

**Virtual Study Procedures**

*1st Virtual Study Visit*

Subjects will provide written informed consent for all study procedures, including the use of text messages, and be enrolled at Brigham and Women's Hospital. The study staff will conduct the consent discussion via video and obtain paperless consent or e-consent from the participant through the MGB approved REDCap e-consent platform. After this visit, they will be mailed an electronic pill bottle manufactured by Pillsy along with written instructions for setup (see Attachments), which participants will be asked to use for the duration of the study. Based on data from prior trials, poorly-controlled patients with type 2 diabetes take an average of two oral glucose-lowering medications, and we expect to distribute approximately two EDMs per patient but no more than three.

At the baseline visit, we will also collect some basic information from subjects to administratively manage the study: name, address, email address, telephone number and the best times and days to contact, in addition to sociodemographic information (see demographics baseline questionnaire). For the patient to complete the surveys in the REDCap database, we will provide them with a secure link to the online database so they can complete the surveys at their convenience. The survey invites will be sent via secure email or SMS using the Twilio platform, a third-party web service integrated into REDCap, which will provide the participant with the survey URL, depending on patient preference. We will review contact information with subjects at each study visit to make sure that we have the most accurate information. Contact information will be stored in the password-protected REDCap database.

Additional information on demographics, diagnoses, medications, comorbidities, laboratory tests and disease activity will be abstracted from participants' medical records. Data will be collected through chart review as well as RPDR and entered into our REDCap database.

Before beginning follow-up, subjects in both arms will be contacted within 2 business days to review procedures, confirm the functionality of their bottles, and verify cellphone numbers for delivery of the intervention.

*Optional Check-in*

Participants will receive their Pillsy electronic pill bottle in the mail along with written instructions on how to setup and use of the Pillsy bottle. They will also be provided with contact information for assistance from the study staff to properly setup their electronic pill bottle. The Pillsy bottle works as a standard pill bottle in which participants will store their medications. To ensure that real-time data is transmitted to the Pillsy server, participants will also download the Pillsy mobile application on their phone that will be connected by Bluetooth to their electronic pill bottle. Participants will not otherwise be asked to engage with the mobile application. Before beginning follow-up, subjects in both arms will be contacted to review procedures, confirm the functionality of their bottles, and verify cellphone numbers for delivery of the intervention.

*Trial Period*

Participants will be asked to use the electronic pill bottle for 6 months. As participants receive medication refills, they will transfer their pills to the Pillsy electronic pill bottle. Throughout the study, participant medication use data will be captured by the electronic pill bottles. The Pillsy electronic pill bottles employ electronic date/time stamp technology that is triggered by opening the pill bottle. Dates and times of bottle opening (and therefore adherence) are transmitted by Bluetooth to the patient's phone through the Pillsy mobile application.

The mobile application data will be automatically transferred to a secure, password-protected Pillsy portal hosted on a secure server located outside of BWH. These uploaded data will be de-identified, except for bottle opening dates and times. Participants will be assigned a study-specific ID, and the electronic bottles will only be linked to this participant by the study-specific ID. These data will only be accessible to the MGB researchers with password-protected access to the Pillsy portal. The only potentially identifiable data in the Pillsy portal are bottle opening dates, times, and study-specific ID.

Patients in the reinforcement learning arm will receive text messages based on their EDM-measured adherence. Based on patient's fixed characteristics and time-varying responses to the messages, the algorithm will determine which text message to send and adapt over time to the messages that individual patients most respond to. The learning algorithm will be re-run daily based on recent adherence patterns and will deliver text messages based on those patterns. Patients in the usual care arm may receive up to daily, untailored text messages.

Patients in both arms may receive disconnectedness text messages, spaced three days apart, if their pill bottles become disconnected from their Pillsy mobile application for longer than a week. Study staff may call patients up to two times, spaced two weeks apart, if their pill bottles become disconnected from their Pillsy mobile application for longer than two weeks. If patients remain disconnected for the rest of the study period, study staff may call patients to reconnect their pill bottles at the end of the study.

The reinforcement learning algorithm will be periodically updated by sending completely de-identified modeling data to a Microsoft server. No patient identifiers will be included in any data on the Microsoft Azure server, only study-specific ID. This server will only be accessible by study staff. To update the reinforcement learning prediction model, study staff will manually upload and download data from the algorithm from the server. To do so, first, study staff will create a spreadsheet with 7-day adherence data from the Pillsy portal onto a MGB computer. This spreadsheet will include EDM-measured adherence as binary indicators (yes/no) for the past 7 days (i.e., dates/times will be removed). Then, study staff will upload this spreadsheet into the reinforcement learning algorithm model. The algorithm will then send fully de-identified data back to the MGB server with its updated prediction information about which type of text to send for each intervention subject. Study staff will then log onto the secure text messaging vendor system already used by MGB to schedule the correct text for each participant for the next day.

The texts will be sent by a secure messaging system vendor, SMS D365 Solution. The Health Innovation Platform team, part of MGB Personalized Medicine and the Digital Care Transformation/Enterprise Data and Digital Health Initiative, built this platform that enables sending and receiving of SMS messages to patients. The application is built on Microsoft's Power Platform using Dynamics 365. The HIPAA-compliant platform can store all incoming and outgoing messages in relational databases. If the patient replies to the text message that does not prompt a reply, they will receive an automated message telling them that the text message system is not monitored by a live individual and instructing them, in the case of the need for urgent medical attention, to call 911, go to their nearest emergency department or calling the 24-hour nurse helpline for their BWH diabetes care practice. For those text messages that elicit a reply from the patient, automatic action will be programmed with messages as follows:

| **Patient Response** | **Automated action or text back to patient** |
|---|---|
| Stop | <Stop text messages> |
| Quit | <Stop text messages> |
| Thank you | <No response> |
| Thanks | <No response> |
| Ok | <No response> |
| <Any other response> | The message you just replied to was automated, so if you need medical help, please contact your 24-hour nurse helpline, call 911, or go to your nearest emergency department. |

*2nd Virtual Study Visit*

At the 2nd study visit, participants will be offered a $50 Amazon gift card that will be mailed to them upon study completion, and they will be able to keep their Pillsy EDM device(s) for personal use. Participants will also be asked to complete a questionnaire about their self-reported medication use and adherence and perspectives on the intervention (if applicable) or EDM monitors. In order for the patient to complete the surveys in the REDCap database, we will provide them with a secure link to the online database via SMS sent through the Twilio platform or via secure e-mail at the patient's discretion.

**In-Person Study Procedures (if/when COVID-19 precautions are lifted – this entire study can be done virtually):**

*1st Study Visit*

At the first study visit, subjects will provide written informed consent for all study procedures, including the use of text messages, and be enrolled at Brigham and Women's Hospital. In this visit, they will be given an electronic pill bottle manufactured by Pillsy, which participants will be asked to use for the duration of the study. Based on data from prior trials, poorly-controlled patients with type 2 diabetes take an average of two oral glucose-lowering medications, and we expect to distribute approximately two EDMs per patient but no more than three.

Participants will then be instructed by a trained study staff member on how to use the Pillsy bottle. The Pillsy bottle works as a standard pill bottle in which participants will store their medications. To ensure that real-time data is transmitted to the Pillsy server, participants will also download the Pillsy mobile application on their phone that will be connected by Bluetooth to their electronic pill bottle. Participants will not otherwise be asked to engage with the mobile application.

At the baseline visit, we will also collect some basic information from subjects to administratively manage the study: name, address, email address, telephone number and the best times and days to contact, in addition to sociodemographic information (see demographics baseline questionnaire). These questionnaires will be completed on paper copies then uploaded to the REDCap databases. If a patient wants to complete the surveys at a later time, we will provide them with a secure link to the online database so they can complete the surveys at their convenience. If so, the survey invites will be sent through secure email via Twilio, a third-party web service integrated into REDCap which will provide the participant with the survey URL through SMS. We will review contact information with subjects at each follow up visit to make sure that we have the most accurate information. Contact information will be stored in the password-protected REDCap database.

**Additional information on demographics, diagnoses, medications, comorbidities, laboratory tests and disease activity will be abstracted from participants' medical records. Data will be collected through chart review as well as RPDR and entered into our REDCap database.**

Before beginning follow-up, subjects in both arms will be contacted within 2 business days to review procedures, confirm the functionality of their bottles, and verify cellphone numbers for delivery of the intervention.

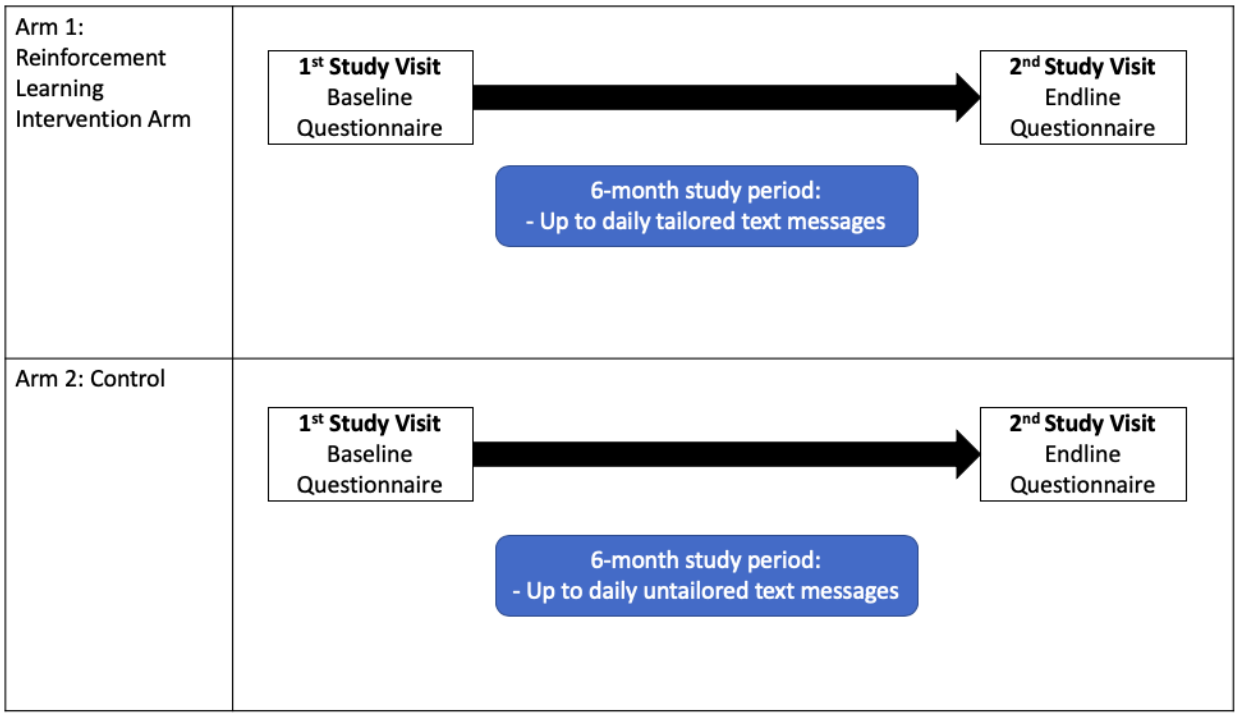
*Trial Period*

The trial period protocol for the in-person study participants is exactly the same as the protocol for the virtual study participants described above.

*2nd Study Visit*

At the 2nd study visit, participants will be offered a $50 Amazon gift card, and they will be able to keep their Pillsy EDM device(s) for personal use. Participants will also be asked to complete a questionnaire about their self-reported medication use and adherence and perspectives on the intervention (if applicable) or EDM monitors.

**Study Schema**




**Outcomes**

The trial's primary outcome is medication adherence assessed in the 6 months after randomization. Medication adherence will be measured by averaging daily adherence (as described above) for each medication across each patient beginning the day after randomization until 180 days after randomization. Secondary outcomes include change in glycemic control as assessed using HbA1c, and self-reported adherence at the end of follow-up. HbA1c values will be collected from routine measurements recorded in the EHR system; we will use the value closest to each patient's 6-month end of follow-up, up to 1 month after

randomization. In routine care, HbA1cs are measured approximately every 3-6 months, so we expect only modest missingness, as we have observed also in prior work. Self-reported adherence will be assessed as the proportion of patients who are adherent according to a validated 3-item self-report measure and prior literature from the follow-up questionnaire.[31] We will also descriptively measure implementation outcomes informed by the RE-AIM framework[53], including representativeness of patients in the study, text messaging opt-out rates, any feedback from patients, and rates of pill bottle disconnectedness, which will inform considerations for how to scale the intervention to other settings.

**Statistical Analysis**

We will report means and frequencies of pre-randomization variables separately by intervention and control arm, comparing these values using absolute standardized differences. The outcomes will be evaluated using intention-to-treat principles among all randomized participants. In the primary analysis, we will evaluate adherence and glycemic control using generalized estimating equations with an identity link function and normally distributed errors. We will also adjust for the block randomized design. We do not expect any missing data for the primary outcome, but may have up to 25% missingness for the glycemic control outcome. If >10% of participants have missing HbA1c data, we will repeat our analyses using multiple imputation. A similar approach will be taken for self-reported adherence, except using a log link function and Poisson distributed errors to generate relative risks of the proportion of adherent patients in the intervention versus control arms. In secondary analyses, we will control for any differences in baseline variables between the arms despite randomization.

As a sensitivity analysis, we will censor patients in the analysis when they have stopped using the electronic pill bottle for >30 days. We will also evaluate the change in HbA1c from baseline until the end of follow-up and differences in self-reported adherence separately for the 3 items that make up the self-reported scale we are using. For glycemic control (HbA1c) and self-reported adherence, we will also conduct complete case analyses. Similarly, subgroup analyses will include stratification by age, sex, race/ethnicity, baseline HbA1c, baseline self-reported adherence, and number of study medications.

Our study should be sufficiently powered to detect clinically meaningful differences in the primary outcome. With 60 subjects, we estimated that we would have the power to detect a 10% difference in average adherence over the 6-month follow-up period between the 2 arms, assuming a standard deviation (SD)=12.5%, power=0.8, and alpha=0.05. With this sample size, we would also be able to detect an HbA1c difference of 1.0% between arms (assuming SD=1.3) and 50% relative difference in self-reported adherence.

**Risk and Discomforts**

We believe that the risks to participation for subjects are no more than minimal. We do not anticipate the occurrence of any incremental adverse events as a result of patients receiving

adherence support for medications that they were already prescribed and for which providers have ultimate oversight. The study team will not be providing any direct care to patients, and all treatment decisions will ultimately be made by the patients' medical teams at MGB. Any adverse events will be handled in the course of regular clinical care. We will also obtain their written informed consent for participation for the trial and for the use of their data in secondary analyses of patient clusters of responsiveness. Finally, we will also safeguard any identifiable information in accordance with IRB practices, limit access to any information in accordance with IRB practices, limit access to the information to study team members actively involved in the research who have all undergone human subjects research training and destroy any information upon completion of the research.

There is a risk that participant medication use data or phone number could be made public if Pillsy's MGB's SMS D365 Solution, or the virtual video visit platform's servers are compromised. However, since the data are not linked to another identifier, the risks of identification remain low. Such an event could lead to embarrassment or other forms of discomfort related to public exposure of health data.

If patients currently use a pillbox for their medications, there is a hypothetical and small risk that using electronic pill bottles during this study could change their daily medication-taking routines, but this has not been verified in any peer-reviewed study.

**Potential Benefits**

This study is designed to improve medication adherence for patients with diabetes. The patient subjects may benefit from improved medication adherence through improved clinical outcomes. The patient subjects will also receive compensation for their participation.

The patient subjects and society may also benefit in the future from accumulated knowledge that originates from this research. The potential societal benefits outweigh the minimal risk, especially in light of multiple measures in place to protect confidentiality. We will also produce several reinforcement learning tool deliverables for this work for the public, researchers, and policymakers, which will be shared as generalized knowledge. These deliverables include the results from the study, text messages, and a potential reinforcement learning algorithm that can be used in a clinical setting to promote medication adherence.

**Monitoring and Quality Assurance**

The research subjects in this study will be subject to no more than minimal risk and we do not anticipate the occurrence of any adverse events. Safety will be assessed during enrollment and the study period. The data obtained from the electronic pill bottles will be monitored weekly by research staff to ensure safety of the subjects. Use of an electronic pill bottle is non-invasive and carries little potential for harm, so it is unlikely the study will need to be stopped.

Relevant clinical data on patients will be retrieved from the electronic medical records at BWH. The data extracts obtained from the electronic medical record are continuously used by clinical operations staff for quality assessment and improvement, and undergo routine, rigorous peer-review by experienced data analysts to ensure accuracy and completeness. The principal

investigator will work with the research project staff to ensure the accuracy of these data throughout the study period.

General oversight of this study is by the principal investigator. There will be regular meetings and contact with research staff to ensure appropriate oversight of all aspects of the study. De-identified study data will always be accessible for the principal investigator and co-investigators to review, if applicable. The principal investigator and co-investigators will also ensure that all protocol deviations are reported to the NIH and the IRB according to the applicable regulatory requirements. Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Data quality will be assessed by study staff continually throughout the course of the study. The electronic pill bottles will automatically upload data, in real time, to Pillsy's servers. This will allow study staff to receive real-time updates on data quality during the study.

Risks incurred by partnering with Pillsy and using MGB's SMS Dynamics 365 platform will be evaluated by the Research Information Security Office. We will ensure compliance with all MGB security requirements through the signing of Master Service Agreements that ensure patient privacy is protected.

We will be in routine contact with the medical leadership at each diabetes clinic to obtain any feedback from clinicians regarding the study (Dr. McDonnell). Our plan for data and safety monitoring also includes oversight by the project principal investigator (Dr. Lauffenburger) throughout the study period.

**Per previous correspondence with RISO for other studies, we will do the following to protect the security of our data:**

- MGB REDCap will be used
- Should any emails be sent to participants, the blind copy function (BCC) must be used when sending to more than one patient/research subject, in order to protect the confidentiality of recipients
- Access to web portal by study staff requires a username and password:
    - Passwords must be a minimum of 8 characters
    - Passwords must be alphanumeric, containing at least one of each.
    - Cannot reuse 4 previous passwords.
    - Passwords must be changed immediately if either the password or the system is or may be compromised
    - Passwords must not be displayed in clear text when they are being input into an application.
    - Passwords must be changed every 90 days
    - Users must be uniquely identified; no shared or group accounts without security authorization
    - Passwords may not be shared
    - User access must be terminated immediately upon termination or change of responsibilities

    - Passwords should not be the same used as regular MGB credentials for workstations
- Only MGB Workstations / Laptops in use for the research
    - Password requirements from above
    - Encryption at rest is in place
    - Up-to-date malware protection including antivirus, spyware detection and removal tools
    - Personal firewall is enabled
    - Manufacturer supported operating system with current updates, if available for the device
    - Crowdstrike End Point protection installed