Using Cues and Rewards in Patients with Arthritis and Rheumatic Disease

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Background and Significance

Non-adherence to evidence-based prescription medications results in preventable morbidity and mortality for middle-aged and older adults. For example, in the case of arthritis, which is the most common cause of disability in the US and the 4th most common condition among Medicare beneficiaries; adherence to evidence-based treatments, is extremely poor and contributes to racial/ethnic, socioeconomic, and gender disparities. Numerous interventions have been tested to help patients adhere to their prescribed therapies ranging from the use of reminder devices, cellphone applications, financial incentives, and pharmacist-led behavioral interviewing. Unfortunately, even the most effective of these approaches have been only modestly effective and when removed, adherence often falls back to baseline.

Taking medications intended for daily use, like those to prevent or treat chronic conditions, is a repetitive action that has great similarity with other behaviors that must be performed consistently, such as regular exercise, healthy eating and hand washing. In these cases, people who consistently act in healthy ways do so out of habit. Formally, a habit is an automated response disposition that is cued by aspects of its performance context (such as the environment in which it occurs or actions that precede it). In this context, habits are learned through a process in which repetition incrementally tunes cognitive processors in procedural memory, or equivalently, habits represent context-response associations in memory that develop as people repeat behaviors in daily life.

The “repetition-cue-reward” model of habit formation has obvious applicability to medication taking, which is a daily repetitive activity. Existing evidence supports the benefits of reminder cues for adherence, such as those using text messaging, as well as rewards in the form of copayment elimination or daily lotteries. However, medication adherence has notable differences. For example, consistently taking preventive medications seldom have obvious symptomatic benefits, particularly short-term benefits that patients can easily attribute to the medications themselves. Further, context cues, such recommending that patients put their medications beside their toothbrush or coffee pot, are insufficient to motivate behavior change for many, and thus more effective tailoring or more potent strategies need to be developed. Accordingly, we plan to adapt the “cue-reward” methodology to improve adherence to rheumatic disease medications.

Specific Aims

This pilot aims to evaluate the feasibility and effectiveness of using the repetition-cue-reward model of healthy habit formation to improve medication adherence in patients with arthritis and rheumatic disease. To accomplish this Aim, this project consists of two phases. **This present protocol focuses only on the second phase, which consists of a small, pragmatic randomized clinical trial.** Due to the current COVID-19 related concerns, this study can be conducted entirely virtually until system-wide policies allow in-person study visits to resume or if the patient does not feel comfortable with in-person study visits.

This phase has the following Aim: *"To determine whether strategies that couple context cues and rewards improve adherence to medications."* We will conduct a 3-arm randomized controlled trial to determine the feasibility, acceptability and effectiveness of motivating consistent medication use with the application of the cue-reward model of habit formation.

The overarching goal of this phase is to understand what context cues and rewards can be used to help patients form long-lasting healthy habits, such as taking their medication(s). By conducting this randomized control trial, we will test potential cues and rewards that can be leveraged to positively impact medication-taking behavior in patients with arthritis and other rheumatic diseases.

Subject Selection

Phase 2: Randomized controlled trial

- We will enroll 70 male and female English-speaking patients receiving their care at a BWH-affiliated rheumatology or primary care practice who have not opted out of being contacted for research, ≥18 years of age with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or gout who are prescribed ≥1 oral medication for this disease for ≥4 months and take this (these) medication(s) independently. For patients with gout, their most recent uric acid value collected in the past 18 months must be >6. For patients with SLE, their most recent c-reactive protein level collected in the past 18 months must be >10. To be included, patients must have the ability to set up the platform and adhere to study procedures.
- Patients will be enrolled in a randomized controlled trial. Patients will be asked to use the Pillsy electronic pill bottle for 5 months. 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. Throughout the 6-month study period, the electronic pill bottles will record medication use.
- Patients will be randomized to one of 3 arms. Patients in the first intervention arm will choose an event-based cue and receive text messages reminding them of their cue up to every four days. Patients in the second intervention arm will start by establishing their cue and having the donation made, but only those who show no improvement in adherence after 6 weeks will start receiving the text messages. In both interventions arms, a donation

will be made to a local charity every time they take their medication. Patients in the control arm will not receive any intervention (but will receive pill bottles to monitor their adherence).

- At the end of the 6-month study period, participants will complete a survey.

At this time, we are only requesting IRB approval for the randomized controlled trial portion of our study (Phase 2 described above). Other phases of the study described in the "Specific Aims and Research Strategy" attachment are not under consideration at this time.

Subject Enrollment

We plan to use 4 sources to identify 70 English-speaking patients ≥18 years of age with RA, lupus, or gout who are prescribed ≥1 oral medication this disease for ≥4 months. For patients with gout or lupus, we will aim to enroll patients with uric acid levels >6 or c-reactive protein levels >10 respectively, in the prior 18-month period.

First, we will use the Brigham Rheumatoid Arthritis Sequential Study (BRASS) and Lupus registries of RA patients actively receiving their care at BWH. We will reach out to the identified patients' rheumatologist for their approval to send them a letter on their behalf inviting them to participate or asking them to introduce the study to their patients with a fact sheet (See Attachments). If the patient is a Patient Gateway user and the patient's rheumatologist gives us approval to do so, we may reach out to them directly through the platform rather than with a letter (see Attachments).

Second, patients will be recruited using advertising to patients visiting clinics and through online registries of patients interested in participating in research projects. Patients will be invited to participate using a flyer, online platforms, a letter, and by patients' care providers. For flyers and platforms, patients will self-identify if interested in participating and will call the study line or contact the study email provided that will be staffed by a research assistant (indicated in this IRB agreement).

Third, we will ask rheumatologists 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 rheumatology practice. We will reach out to the identified patients' rheumatologist for their approval to send them a letter on their behalf inviting them to participate or asking them to introduce the study to their patients with a fact sheet (See Attachments). If the patient is a Patient Gateway user and the patient's rheumatologist gives us approval to do so, we may reach out to them directly through the platform rather than with a letter (see Attachments).

Fourth, we will use both a weekly EPIC screen for patients with upcoming virtual or in-person appointments and RPDR to identify patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and or gout whose condition is managed by a BWH rheumatologist or primary care physician, and who are taking an oral medication for their disease. We will also use RPDR to help determine demographic information, medication use, uric acid levels and c-reactive protein levels. We will reach out to the identified patients' rheumatologist or primary care physician (depending on which provider is responsible for managing the disease) for their approval to send them a letter on their behalf inviting them to participate or asking them to introduce the study to their patients with a fact sheet (See Attachments). For patients whose rheumatic condition is managed by a primary care physician, we will send two separate recruitment letters at once: one signed by a leader of the BWH primary care research network and the other one signed by the study PI. This recruitment strategy is being implemented as a request from the BWH primary care practices. If the patient is a Patient Gateway user, we may reach out to them directly through the platform rather than with a letter (see Attachments).

If patients prefer correspondence to occur, once enrolled, via email, we will do this via Patient Gateway or send secure. We will include the below text in secure emails, 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.

Participants will have 3 study-related visits. These study visits can be completed completely virtually or in-person during clinic visits (if/when COVID-19 precautions are lifted). To cover both possible time windows, both sets of procedures are described in further detail below.

Using a random number generator, the study research assistant will randomize 20 patients to the first intervention arm, 20 patients to the second intervention arm, and 20 patients to the control arm. Other clinic staff and analysts will be blinded to arm assignment. A password-protected, REDCap database will link study-specific ID and participant name.

Study Procedures

1st Virtual Study Visit

At the first study visit conducted using a Partners approved video platform, subjects will provide written informed consent for all study procedures, including the use of text messages, and be enrolled into the study. The study staff will be virtually present for the consent process and will obtain electronic informed consent from the participant using Partners approved REDCap e-consent/paperless consent process.

After this visit, they will be mailed up to 3 electronic pill bottles manufactured by Pillsy along with written instructions for setup. Participants will be asked to use the pill bottle(s) for the duration of the study. 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 via secure email. 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.

2nd Virtual Visit: Device Setup

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 (see Attachments). 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 5 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 Partners 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.

- Arm A: Non-adaptive intervention

  Patients in the first intervention arm will participate in a goal-setting exercise during which they will identify which habit they want to link their medication-taking to (see Attachments). For example, a patient who takes their medication in the morning may elect to link tooth brushing with medication taking. If a patient is non-adherent, patients will receive a text message up to every 4 days reminding them of the habit they decided to link to their medication-taking (see Attachments).

  Patients in the first intervention arm will also select a charity to which a donation will be made every time the bottle is opened. The research team will donate $0.50 every day that the patient takes their medication as prescribed. Patients will pick between the charities below:

- Animal Rescue League of Boston
- UNICEF
- Greater Boston Area Food Bank

A research assistant will place a sticker with the charity logo under pill bottle cap so that the patient is reminded of the donation every time they take the medication (see Attachments). Additionally, the patient will receive texts every 4 days summarizing how much money was donated on their behalf.

- Arm B: Adaptive intervention

Patients in the second intervention arm will participate in a goal-setting exercise during which they will identify which habit they want to link their medication-taking to. For example, a patient who takes their medication in the morning may elect to link tooth brushing with medication taking.

Patients in the second intervention arm will also select a charity to which a donation will be made every time the bottle is opened. The research team will donate $0.25 every day that the patient takes their medication as prescribed. Patients will pick between the charities below:

- Animal Rescue League of Boston
- UNICEF
- Greater Boston Area Food Bank

A research assistant will place a sticker with the charity logo under pill bottle cap so that the patient is reminded of the donation every time they take the medication (See Attachments). Additionally, the patient will receive texts every 4 days summarizing how much money was donated on their behalf.

After 6 weeks, patients who remain non-adherent will be intensified to receive $0.50 every day they take their medication as prescribed and receive a text message up to every 4 days reminding them of the habit they decided to link to their medication-taking at the start of the intervention (see Attachments).

- Arm C: Control

Patients in the control arm will receive no intervention.

The text messages in Arms A and B 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. If patients communicate any medical concerns that come up during the study, we will contact their provider as needed. 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	You're welcome - keep up the good work!
Thanks	You're welcome - keep up the good work!
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.

Patients in all arms may receive disconnectedness text messages, spaced at least three days apart, if their pill bottles become disconnected from their Pillsy mobile application for three days or longer. 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.

In the event that daily adherence available becomes unavailable due to Pillsy or REDCap system issues, we will continue to send any scheduled text messages regarding cue reminders, end of intervention notices, and end of study notices. However, in lieu of disconnectedness text messages or reward messages, participants who are actively receiving intervention text messages will receive the following 2-part text message every 3 days: "*We are experiencing issues retrieving data about your daily medication taking. Please continue to take your medicine and remain connected to your pill bottle." and "Don't worry! We are hard at work fixing our technical issues, and as soon as we do, we will ensure that your donation to [SELECTED CHARITY] is made.*"

Participants will be offered a $50 Amazon gift card code that will be texted to them via Dynamics 365 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 Dynamics 365 platform or via secure e-mail at the patient's discretion. Study staff may call patient up to three times to ensure survey completion.

After completion of the study, the study team will conduct exit interviews with 15 participants with varying demographics, medication adherence and study arm participation to understand their experiences participating in the study and what may (or may not) have worked for them. This will be conducted via telephone and is estimated to take 5-10 minutes. Responses will be written down as notes by the caller.

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 Partners Healthcare. 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 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.

Potential Benefits

This study is designed to improve medication adherence for patients with RA, lupus, or gout. The patient subjects may benefit from improved medication adherence through improved clinical outcomes. They will also be provided with their adherence patterns at the end of the study period that they can share with their rheumatologist or primary care physician if they wish. The patient subjects will also receive compensation for their participation in the trial.

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 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 strategies that can be used in a clinical setting to promote medication adherence.

Monitoring and Quality Assurance

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.

Unanticipated problems involving risks to subjects or other problems including adverse events will be reported to the PHRC in accordance with the PHRC unanticipated problems including adverse events reporting guidelines.

If any participant experiences what they perceive as an adverse event related to the information provided, the PI will report this to the IRB immediately.

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

- Partners REDCap will be used
- Partners Enterprise Zoom or Jabber will be used to conduct virtual visits.
- 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 Partners credentials for workstations
- Only Partners 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