



# BMJ Open Randomised controlled trial targeting habit formation to improve medication adherence to daily oral medications in patients with gout

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## ABSTRACT

**Introduction** Medication adherence for patients with chronic conditions such as gout, a debilitating form of arthritis that requires daily medication to prevent flares, is a costly problem. Existing interventions to improve medication adherence have only been moderately effective. Habit formation theory is a promising strategy to improve adherence. The cue-reward-repetition principle posits that habits are formed by repeatedly completing an activity after the same cue and having the action rewarded every time. Over time, cues become increasingly important whereas rewards become less salient because the action becomes automatic. Leveraging the cue-reward-repetition principle could improve adherence to daily gout medications.

**Methods and analysis** This three-arm parallel randomised controlled trial tests an adaptive intervention that leverages the repetition cue-reward principle. The trial will begin recruitment in August 2021 in Boston, Massachusetts, USA. Eligible patients are adults with gout who have been prescribed a daily oral medication for gout and whose most recent uric acid is above 6 mg/dL. Participants will be randomised to one of three arms and given electronic pill bottles. In the two intervention arms, participants will select a daily activity to link to their medication-taking (cue) and a charity to which money will be donated every time they take their medication (reward). Participants in Arm 1 will receive reminder texts about their cue and their charity reward amount will be US\$0.50 per day of medication taken. Arm 2 will be adaptive; participants will receive a US\$0.25 per adherent-day and no reminder texts. If their adherence is <75% 6 weeks postrandomisation, their reward will increase to US\$0.50 per adherent-day and they will receive reminder texts. The primary outcome is adherence to gout medications over 18 weeks.

**Ethics and dissemination** This trial has ethical approval in the USA. Results will be published in a publicly accessible peer-reviewed journal.

**Trial registration number** NCT04776161

## INTRODUCTION

Non-adherence to evidence-based prescription medications results in preventable

## Strengths and limitations of this study

- The study uses a randomised controlled trial study design with an adaptive arm to test the effect of a principle-driven cue-reward intervention on medication adherence.
- The intervention is personalised to each participant and their unique cues that might trigger improved adherence.
- Our usage of electronic pill bottles in every arm may increase overall adherence due to the Hawthorne effect and limit our ability to detect a difference between study arms.
- Participants may already use a system of cues and rewards of their own making, which could bias our results towards the null.

morbidity and mortality for middle-aged and older adults.<sup>1-4</sup> Studies have consistently shown that among patients with chronic illnesses, 50% of medications are not taken as prescribed.<sup>1,5</sup> For patients who have gout, the most common chronic inflammatory arthritis in the USA,<sup>6</sup> poor adherence to urate lowering therapy (ULT) is a key reason why patients fail to reach treatment goals and have debilitating arthritis flares.<sup>7</sup>

Barriers to adherence are numerous, and include cost, unwanted side effects, and forgetfulness among many others.<sup>8,9</sup> Interventions to improve adherence have focused on increasing knowledge about the importance of medications<sup>2</sup> or motivation to take medications.<sup>4</sup> Unfortunately, even the most successful of these approaches have been only modestly effective and positive results are generally only seen over the short term.<sup>1,2</sup>

One promising strategy to increase medication adherence in significant and sustainable ways is approaching medication-taking as a

daily habit.<sup>4</sup> Taking a medication every day is similar to other repetitive behaviours that must be performed consistently, such as brushing one's teeth every morning or washing one's hands after using the bathroom. In these cases, people who consistently act in healthy ways do so out of habit.<sup>10 11</sup> The repetition-cue-reward model proposes that habit formation has three central components: behavioural repetition, associated context cues, and rewards.<sup>12 13</sup> Under this model, habits are formed by completing an activity in contiguity with a particular cue, and having the action rewarded. When this sequence is repeated, cues become increasingly important, whereas rewards become increasingly less salient because a level of automaticity has been reached. Once habits are formed, they guide actual behaviour rather than intention.<sup>13</sup> For example, eating habits are stronger determinants of food choices than eating intentions or susceptibility to eating temptations.<sup>14</sup>

Accordingly, principles of habit formation have the potential to improve medication adherence by transforming the act of medication-taking into an automatic action. Therefore, we propose a randomised controlled trial that aims to identify whether an intervention targeting habit formation using the cue-reward repetition model has the potential to improve adherence to chronic, daily ULT in patients with gout.

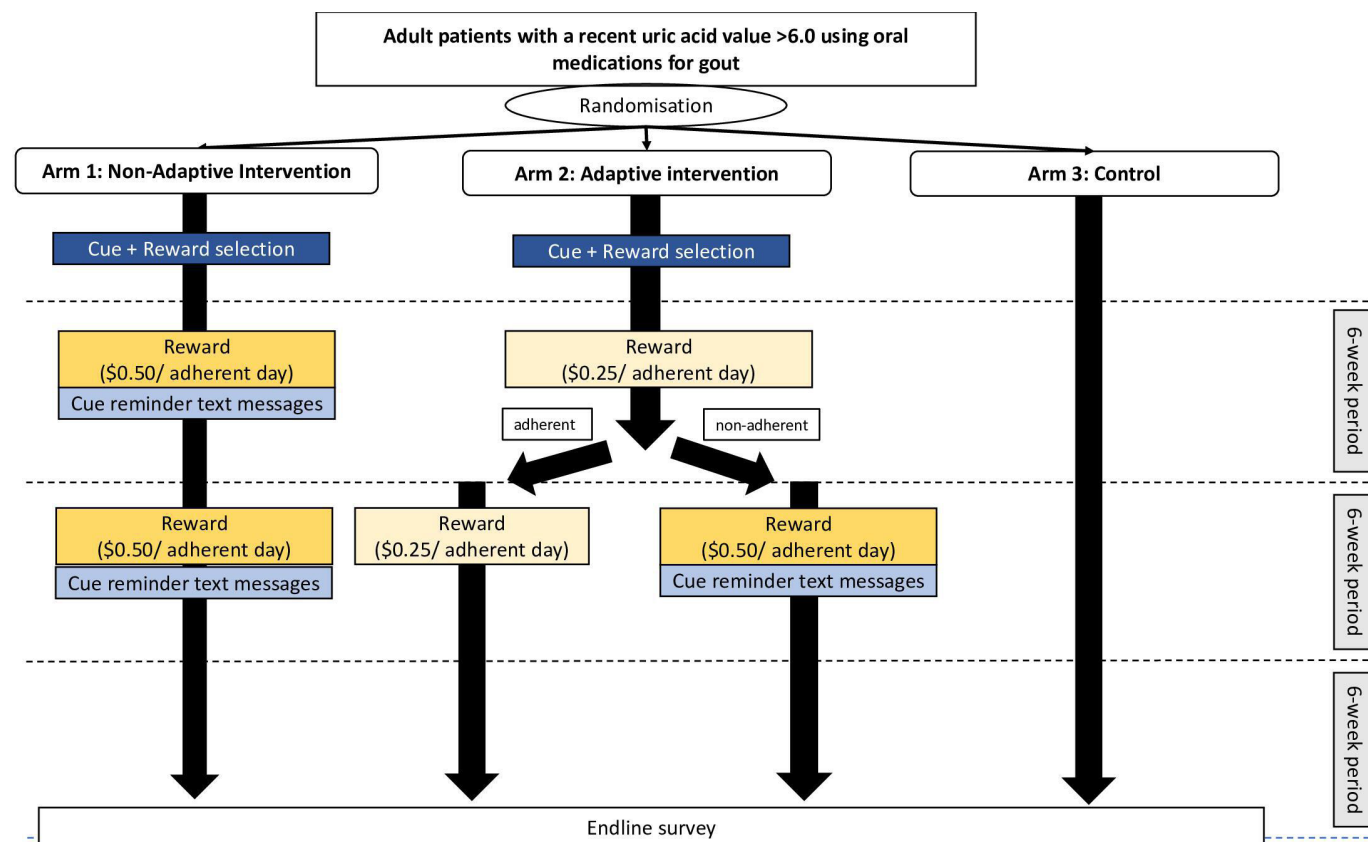
## METHODS

### Study design

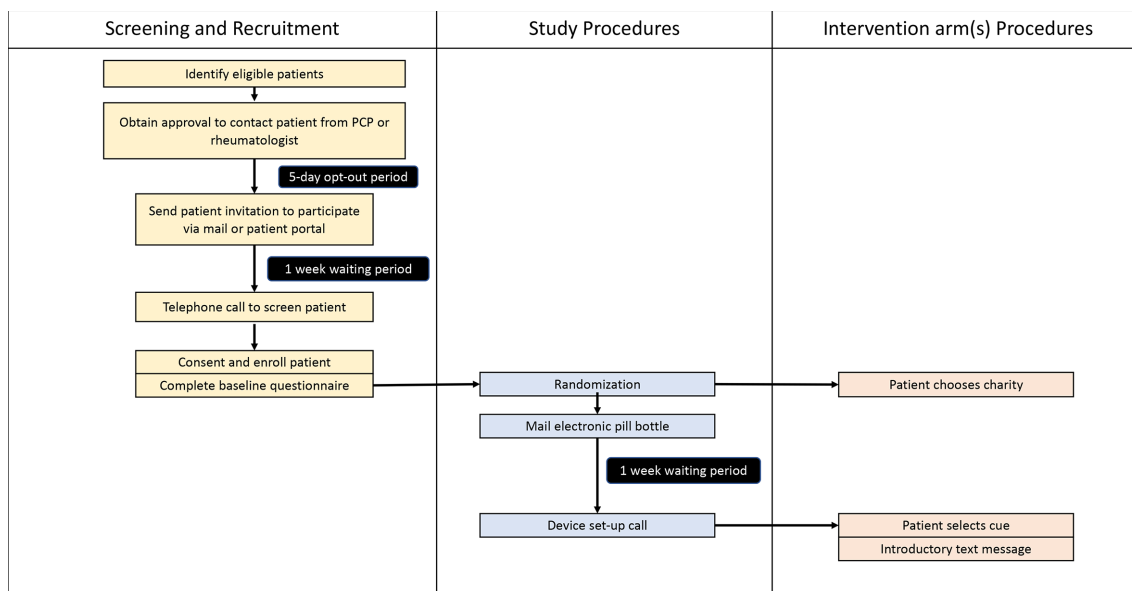
This study is a pragmatic, prospective, three-arm parallel randomised controlled trial designed to evaluate a habit formation intervention for improving adherence to daily ULT among individuals with gout (see figure 1). Enrolment began in August 2021 and we plan to complete follow-up by April 2022.

### Study setting and participants

We will enrol patients who are currently receiving gout care at a rheumatology or primary care practice affiliated with Brigham and Women's Hospital, a large academic medical centre in Boston, Massachusetts, USA caring for over 4000 patients with gout every year. Potentially eligible participants are individuals who are at least 18 years old with gout, who receive a stable dose of oral ULT, and whose most recent uric acid level within the last 6 months is  $>6$  mg/dL (target therapeutic level while on ULT is  $<6$ ). Eligible patients must also have a smartphone with a data plan or WiFi at home and be willing to use electronic pill bottles for their gout medications for the duration of the study. These criteria were chosen because the use of electronic pill bottles requires smartphone connectivity to record adherence. Finally, because the intervention is currently only available in the English language, participants will be required to have a basic working knowledge of English. Patients will be excluded if they are currently pregnant.



**Figure 1** Trial design.



**Figure 2** Screening and recruitment procedures. PCP; Primary care provider.

### Recruitment and screening

Due to social distancing restrictions put in place because of the COVID-19 pandemic, we will screen and recruit participants remotely (see [figure 2](#)). We will identify eligible participants using electronic health record (EHR) data. For patients identified through the EHR, we will first contact the patients' rheumatologist or primary care physician for their approval to approach the patient. If the provider does not opt out an identified patient, the patient will be sent a letter with information about the study inviting them to participate. One week later, patients will be contacted by phone to ask about their interest in the study and to confirm eligibility. If patients agree to participate, they will provide electronic written informed consent for all study procedures, including the use of text messages, and complete baseline questionnaires using REDCap (Research Electronic Data Capture),<sup>15</sup> a secure web-based data collection tool.<sup>16 17</sup> This paperless consent process was approved by our Institutional Review Board. At the end of the enrolment visit, they will be randomised to one of three arms. All participants will then be mailed up to two electronic pill bottles manufactured by Pillsy along with written instructions for setup. Participants in the intervention arm will also be given a guide to assist them in selecting a cue (see online supplemental file 1).

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

### Randomisation

Study enrolment began in August 2021 and is anticipated to be completed by January 2022. In order to improve balance between the three arms, we will use block randomisation stratified by (1) recruitment method, specifically through rheumatology or primary care practices

and (2) baseline uric acid  $>6.0$ – $8.0$  mg/dL or  $>8.0$  mg/dL. Participants will be randomised by research assistants in a 1:1:1 ratio within blocks of three participants to one of three treatment arms using the randomisation module integrated in REDCap.<sup>16 17</sup>

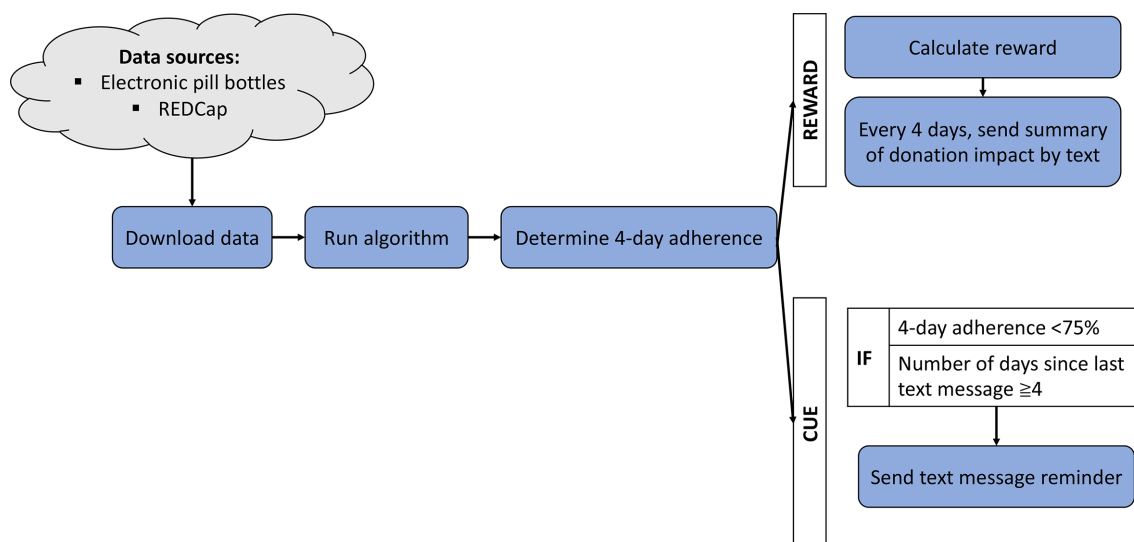
### Interventions

This trial will have two intervention arms and one control arm. Both intervention arms will include a cue-reward 'couplet', but the intensity of the couplet will depend on arm assignment. The study design and intervention components are described further in [figure 1](#).

#### Arm 1: non-adaptive intervention

Participants in the first intervention arm will choose a lifestyle 'cue' and receive a reward over a 12-week period. The cue will be selected by each participant through a goal-setting exercise during which they will identify the activity they want to link to their medication-taking (see online supplemental file 1). For example, a participant who takes their medication in the morning may elect to link tooth brushing with medication-taking. Participants will select their cue assisted by study staff during the device set up call. If adherence falls below 75%, for the prior 4 days, participants will receive a text message reminding them of the cue they decided to link to their medication-taking (see [figure 3](#) and online supplemental file 2).

The 'reward' will consist of a charitable donation every time the participant takes their medication. Participants will choose a charity during the enrolment visit, in specific a local animal shelter, a local food bank, or UNICEF. To clearly link the reward to the act of medication-taking, a sticker with the charity logo will be placed under the patient's pill bottle cap prior to mailing it to the participant so that they are reminded of the donation every time they take their medication (see online supplemental



**Figure 3** Daily procedures. REDCap; Research Electronic Data Capture.

file 3). Every day that the participant takes their medication as prescribed, US\$0.50 will be donated to their charity of choice. Participants will receive texts every 4 days summarising how much money was donated on their behalf and the potential impact of their donation (see online supplemental file 4). For example, participants who chose the local food bank as their charity could receive a text message that states ‘By taking your medication, you helped people struggling with hunger. Thanks to you, the Greater Boston Area Food Bank has been able to prepare eight free meals.’

After the 12-week study period, participants will then be observed for 6 weeks without any intervention.

To determine the amount of the reward and whether a text reminder about the cue needs to be sent, adherence from the prior 4 days will be calculated by dividing the number of times a patient opened the pill bottle by the number of doses expected to be taken over 4 days. For patients on more than one medication, the values for each medication are averaged. Adherence values will range from 0% to 100%. To avoid erroneously classifying repeated bottle openings over a short period of time as multiple unique medication-taking events, we only count a maximum of 1 opening event per 3-hour period; opening events more than 3 hours apart are classified as separate doses.

#### Arm 2: adaptive intervention

Participants in the second intervention arm will receive cues and rewards as with Arm 1 for the first 6 weeks of the study period, although the amount of the reward will be US\$0.25 per day. At the 6-week point, participants who remain non-adherent will be intensified and begin receiving text messages as in Arm 1 reminding them of the activity they decided to link to their medication-taking at the start of the intervention (see figure 3 and online supplemental file 4). They will receive these text messages over the following 6 weeks. Additionally, non-adherent

participants will also see their charity reward increased to US\$0.50 per day to match the non-adaptive intervention arm. Participants will then be observed for 6 weeks without any intervention.

#### Arm 3: control

Participants in the control arm will not receive any intervention but will receive electronic pill bottles to monitor their adherence over 18 weeks.

#### Data collection and management

Participants will be asked to complete surveys at baseline to capture demographic information, medical history, disease activity, and self-reported medication adherence (see online supplemental file 5). Additionally they will complete the Self-Report Behaviour Automaticity Index,<sup>18</sup> which assesses whether participants complete a given activity (such as medication-taking) automatically, for example by asking if they start doing it before they realise they are doing it. We will also use the routine assessment questionnaire developed by Heintzelman and King,<sup>19</sup> which provides a measure of how participants integrate a certain activity into their routine. Additionally, we will inquire about intentions and perceptions of medications using a modified version of the HIV Intention and Knowledge scale.<sup>20</sup> Coexisting medical conditions and uric acid values will be extracted from the patient’s EHR. At the end of the study, participants will be asked to complete a follow-up questionnaire mirroring questions from the baseline questionnaire about medication-taking automaticity, integration of medication-taking into their routine, and intentions and perceptions regarding their medications. In addition, we will ask for feedback regarding the usefulness, acceptability, and feasibility of the intervention. These data will be electronically recorded in a REDCap database. Once recorded, data will be locked to prevent changes. After the end of follow-up, participants



will be compensated with a US\$50 gift card after completion of the survey.

Adherence will be measured using Pillsy electronic pill bottles. These devices will be used in place of participants' regular pill bottles and record the date and time of each bottle opening. Data from the bottles are transferred via Bluetooth to a mobile application on the participant's cell phone. Data from this mobile application are accessible to the research team in near real-time through a cloud-based portal. The set up required for these devices is minimal. Several studies have shown that electronic pill bottles represent a more reliable and accurate method of adherence measurement than self-report.<sup>21</sup> Despite this, monitoring does have theoretical potential to influence adherence itself. To minimise this bias, any added functionality that these devices offer (e.g., alerts when doses are due) will be disabled. Additionally, bias would be non-differential and the observer effects of the devices will decrease over time,<sup>22</sup> as has been observed in other medication adherence studies.<sup>23 24</sup> The use of pill caps will allow us to evaluate objective medication-taking (both to classify patterns and evaluate trial outcomes) over a short period of time.

### Outcomes

The trial's primary outcome is adherence to gout medications over the 18-week follow-up period after randomisation. We will use an average of averages approach,<sup>25</sup> where medication adherence will be measured as the proportion of times a participant opened the electronic pill bottle out of the number of doses prescribed for each bottle in each day, averaged across the study medications and over the follow-up period.

Secondary outcomes will include habit formation through change in automaticity and sense of routine from baseline, as well as possible changes in intention or perceptions of gout medications. Additionally, we will explore the feasibility and acceptability of the intervention within the intervention arms. Exploratory outcomes will include change in uric acid level from baseline. We will use the uric acid level value available in the EHR closest to each participant's end of follow-up date to calculate change in uric acid level. Since uric acid levels may not be collected on a regular basis and may be collected differentially for adherent patients, we expect 15%–20% missing data<sup>26 27</sup> and will consider the results of this analysis exploratory.

### Statistical analysis, sample size and power estimates

We will include all patients randomised in the study in these analyses. We will report the means and frequencies of baseline variables, including demographics, baseline medication use and self-reported adherence, coexisting illnesses and self-reported automaticity separately for the three intervention arms. Comparisons of these values for the two intervention arms to the usual care arm will be performed using t-tests and  $\chi^2$  tests and their non-parametric analogues, as appropriate.

The outcomes will be evaluated using intention-to-treat principles among all randomised participants. Change in mean adherence and mean uric acid level will be analysed using generalised estimating equations with an identity link function and normally distributed errors. If there are differences in baseline characteristics between study groups, we will repeat our analyses after adjusting for these covariates. If a substantial amount of subjects have missing outcome data, we will repeat our analyses using the latest postrandomisation lab values available and using multiple imputation.<sup>28</sup>

We powered the study to detect a clinically meaningful 20% relative increase in adherence between each intervention arm and our control arm. We estimated that we would have 80% power at an alpha threshold of 0.05 to detect this effect by randomising 20 participants to each arm, assuming that the baseline rate of adherence to urate-lowering therapy in our patient population is 50%. Data will then be analysed with SAS V.9.4. Access to the deidentified data sets will be limited to the study authors.

### Patient and public involvement

We used electronic pill bottles to monitor medication use in a previous qualitative study among patients with gout to learn more about their experiences with taking daily oral medications. These interviews helped inform the design of our intervention.

### DISCUSSION

A habit is an action that is triggered automatically in response to a contextual cue. For example, getting into a car can be the contextual cue for the action of putting on a seatbelt. Once habits are formed, conscious attention to the action diminishes as automaticity takes over. Habit formation theory is a promising strategy to improve medication adherence, as medication-taking is a daily repetitive behaviour that could be associated to contextual cues through the cue-reward-repetition model. We propose this trial to test the impact of a habit formation intervention on adherence to urate-lowering therapy (ULT) for patients who suffer from gout. ULT are chronic daily medications that do not provide immediate symptom relief but rather reduce the likelihood of debilitating flares of inflammatory arthritis caused by gout, if taken consistently, as prescribed.

Habit formation theory has already had practical implications for health promotion. For example, a randomised controlled trial of a low-intensity habit formation intervention for weight control led to increased weight loss maintained over time.<sup>29</sup> We hypothesise that creating a system of cues and rewards for patients can increase automaticity of medication-taking and improve adherence to oral medications intended for daily use. We anticipate that this study will also help reduce gout flares.

There are a few limitations to this study. First, we will enrol patients who have access to a cell phone. While cell phone usage is almost ubiquitous in the USA,<sup>30</sup> there

are still individuals without one who would not be able to participate, which may limit the generalisability of the study. Second, while we will measure adherence outcomes after the intervention has been removed for 6 weeks, we will be measuring short-term outcomes and are therefore unable to understand the long-term effects of our intervention. Finally, the use of electronic pill bottles and frequent text messages may result in a Hawthorne effect, although we expect the effect to decrease over time and be non-differential across groups. Similarly, while patients in the control group may already have a cue in place that triggers medication-taking, we expect that most patients enrolled will be non-adherent as we are requiring an elevated uric acid, which may suggest suboptimal ULT use. Randomisation will also limit any bias.

In conclusion, this trial will evaluate the impact of an individually-tailored habit formation intervention to improve adherence to daily medications for patients who suffer from gout. If the intervention is effective, this strategy could be tested in and scaled to other diseases, clinical environments, and health behaviours.

## ETHICS AND DISSEMINATION

This protocol has been approved by the Institutional Review Board at Brigham and Women's Hospital. No data monitoring committee was deemed necessary by the human subjects' oversight boards. Written informed consent will be obtained from all participants. Data analysts at the end of the study will be blinded to arm assignment; however, patients are not blinded due to the nature of the interventions. The findings from this work will be published in a peer-reviewed journal and publicly accessible.

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