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A Randomized Controlled Trial Targeting Habit Formation to Improve Medication Adherence to Daily Oral Medications in Patients with Gout

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A RANDOMIZED 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 3-arm parallel randomized controlled trial tests an adaptive intervention that leverages the repetition cue-reward principle. The trial will begin recruitment in July 2021 in Boston, MA. 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 randomized 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 $0.50 per day of medication taken. Arm 2 will be adaptive; participants will receive a $0.25 per adherent-day and no reminder texts. If their adherence is <75% 6 weeks post-randomization, their reward will increase to $0.50 per adherent-day and they wil receive reminder texts. The primary outcome is adherence to gout medications over 18 weeks.

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

Registration details: clinicaltrials.gov(NCT0477616)

ARTICLE SUMMARY

Strengths and limitations

- The study uses a randomized 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 personalized 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.

INTRODUCTION

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

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

One promising strategy to increase medication adherence in significant and sustainable ways is approaching medication-taking as a daily habit.[4] Taking a medication every day is similar to other repetitive behaviors 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.[10, 11] The repetition-cue-reward model proposes that habit formation has three central components: behavioral repetition, associated context cues and rewards.[12, 13] 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 behavior rather

than intention[13]. For example, eating habits are stronger determinants of food choices than eating intentions or susceptibility to eating temptations.[14]

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 randomized 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 randomized controlled trial designed to evaluate a habit formation intervention for improving adherence to daily ULT among individuals with gout (see Figure 1). The trial is funded by the National Institute on Aging and is registered on ClinicalTrials.gov (NCT0477616). Enrollment will begin in July 2021 and we plan to complete follow-up by April 2022.

Study Setting and participants

We will enroll 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 center in Boston, MA caring for over 4,000 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. for list of eligible oral medications), 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.

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 through 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 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 the REDCap electronic data capture tool. [15, 16] This paperless consent process was approved by our Institutional Review Board (IRB). At the end of the enrollment visit, they will be randomized to one of 3 arms. All participants will then be mailed up to 2 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 **Supplement 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.

Randomization

Study enrollment will begin in July 2021 and is anticipated to be completed by December 2021. In order to improve balance between the 3 arms, we will use block randomization 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 randomized by research assistants in a 1:1:1 ratio within blocks of 3 participants to one of 3 treatment arms using the randomization module integrated in the REDCap electronic data capture platform.[15, 16]

Interventions

This trial will have 2 intervention arms and 1 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 to which activity each individual wants to link their medication-taking (see **Supplement 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 assited 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 **Supplement 2**).

The 'reward' will consist of a charitable donation every time the participant takes their medication. Participants will choose a charity during the enrollment visit, in specific a local animal shelter, a local food bank, and UNICEF. To make the reward more proximal 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 **Supplement 3**). Every day that the participant takes their medication as prescribed, $0.50 will be donated to their charity of choice. Participants will receive texts every 4 days summarizing how much money was donated on their behalf and the potential impact of their donation (see **Supplement 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 8 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 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 $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 **Supplement 4**). They will receive these text messages over the following 6 weeks. Additionally, non-adherent participants will also see their charity reward increased to $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 Supplement 5**). Additionally they will complete the Self-Report Behavior Automaticity Index (SBRAI),[17] which assesses whether participants complete a given activity (such as medication-taking) automatically, for example by asking if they start doing it before they realize they are doing it. We will also use the routine assessment questionnaire developed by Heintzelman et al[18], 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.[19] Coexisting medical conditions and uric acid values will be extracted from the patient's electronic health record. 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 USD50 gift card upon 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.[20] Despite this, monitoring does have theoretical potential to influence adherence itself. To minimize 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[21], as has been observed in other medication adherence studies.[22, 23] 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 randomization. We will use an average of averages approach [24], 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[25, 26] and will consider the results of this analysis exploratory.

Statistical analysis, sample size and power estimates

We will include all patients randomized 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 X^2 tests and their non-parametric analogues, as appropriate.

The outcomes will be evaluated using intention-to-treat principles among all randomized participants. Change in mean adherence and mean uric acid level will be analyzed using generalized 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 post-randomization lab values available and using multiple imputation.[27]

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 randomizing 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 analyzed with SAS 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 behavior 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 randomized controlled trial of a low-intensity habit formation intervention for weight

control led to increased weight loss maintained over time.[28] We hypothesize 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 enroll patients who have access to a cell phone. While cell phone usage is almost ubiquitous in the United States[29], there are still individuals without one who would not be able to participate, which may limit the generalizability 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 effect 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 suggests suboptimal ULT use. Randomization 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 behaviors.

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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AUTHORS' CONTRIBUTIONS

All authors meet International Committee of Medical Journal Editors (ICMJE) criteria. CPF contributed meaningfully to trial or intervention design and implementation and drafted the trial protocol and manuscript. CHF had overall responsibility for the trial design and helped draft the trial protocol and manuscript. NKC is the co-principal investigator, had overall responsibility for the trial design and trial protocol, and helped draft the trial protocol and manuscript. WW, TD, NH, RO, ESS, EK, KH, RAB, and JCL contributed meaningfully to trial or intervention design and implementation as well as the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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COMPETING INTERESTS

Dr. Feldman serves in unpaid positions on the Board of Directors of the American College of Rheumatology and on the Medical-Scientific Advisory Council of the Lupus Foundation of America. She receives research support from Pfizer Pharmaceuticals unrelated to this work. Dr. Choudhry is a consultant to and holds equity in RxAnte, unrelated to this work. He receives grant funding, payable to his institution, from Boehringer Ingelheim and Humana, also unrelated to the current work. Dr. Barlev is funded by an unrestricted educational grant from Boehringer Ingelheim to the Brigham and Women's Hospital, unrelated to the current work.

DATA SHARING STATEMENT

Data will be available upon reasonable request, pending appropriate agreements and Institutional Review Board approval, including patient data and programming code.

PATIENT CONSENT FOR PUBLICATION

Not required

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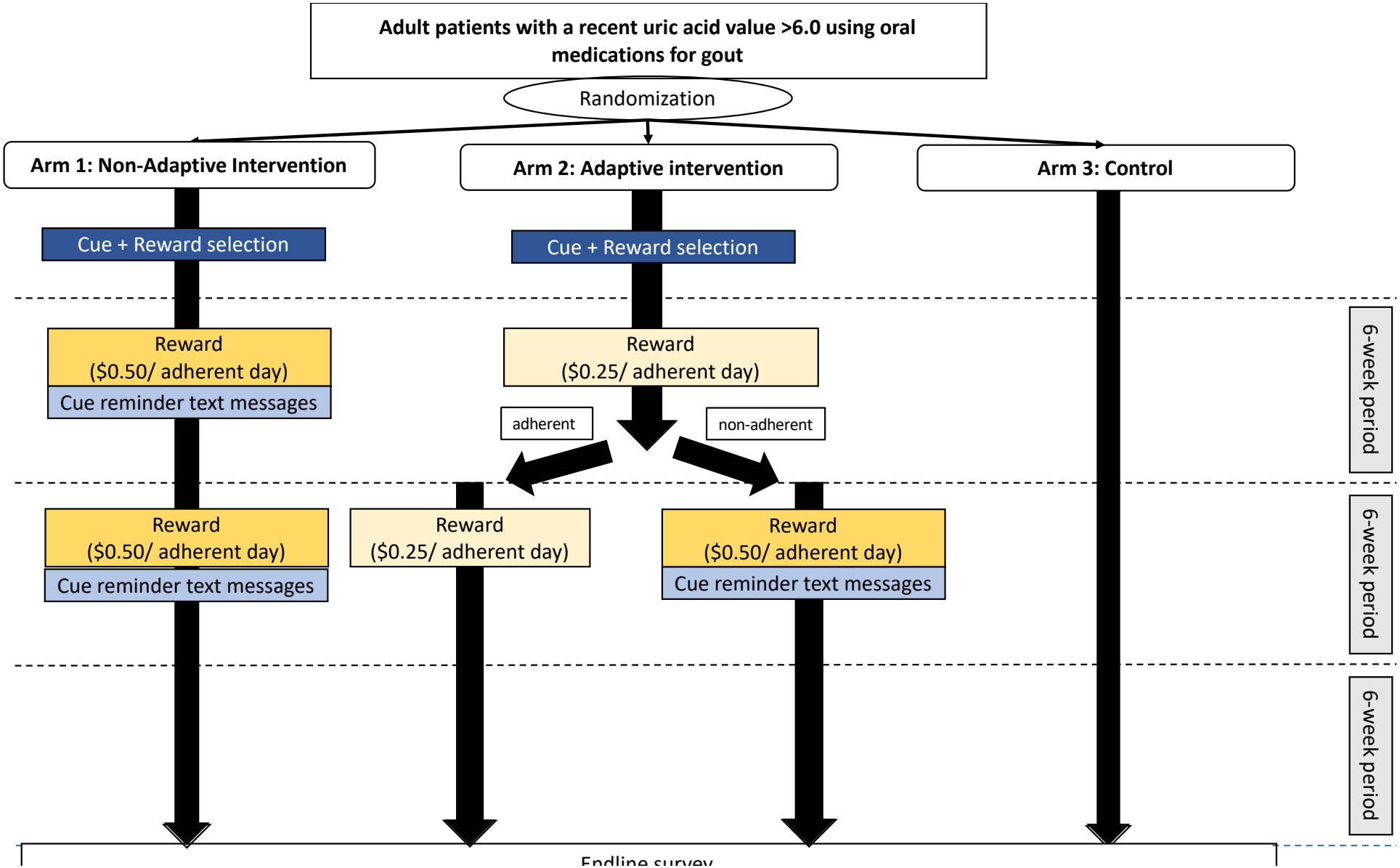
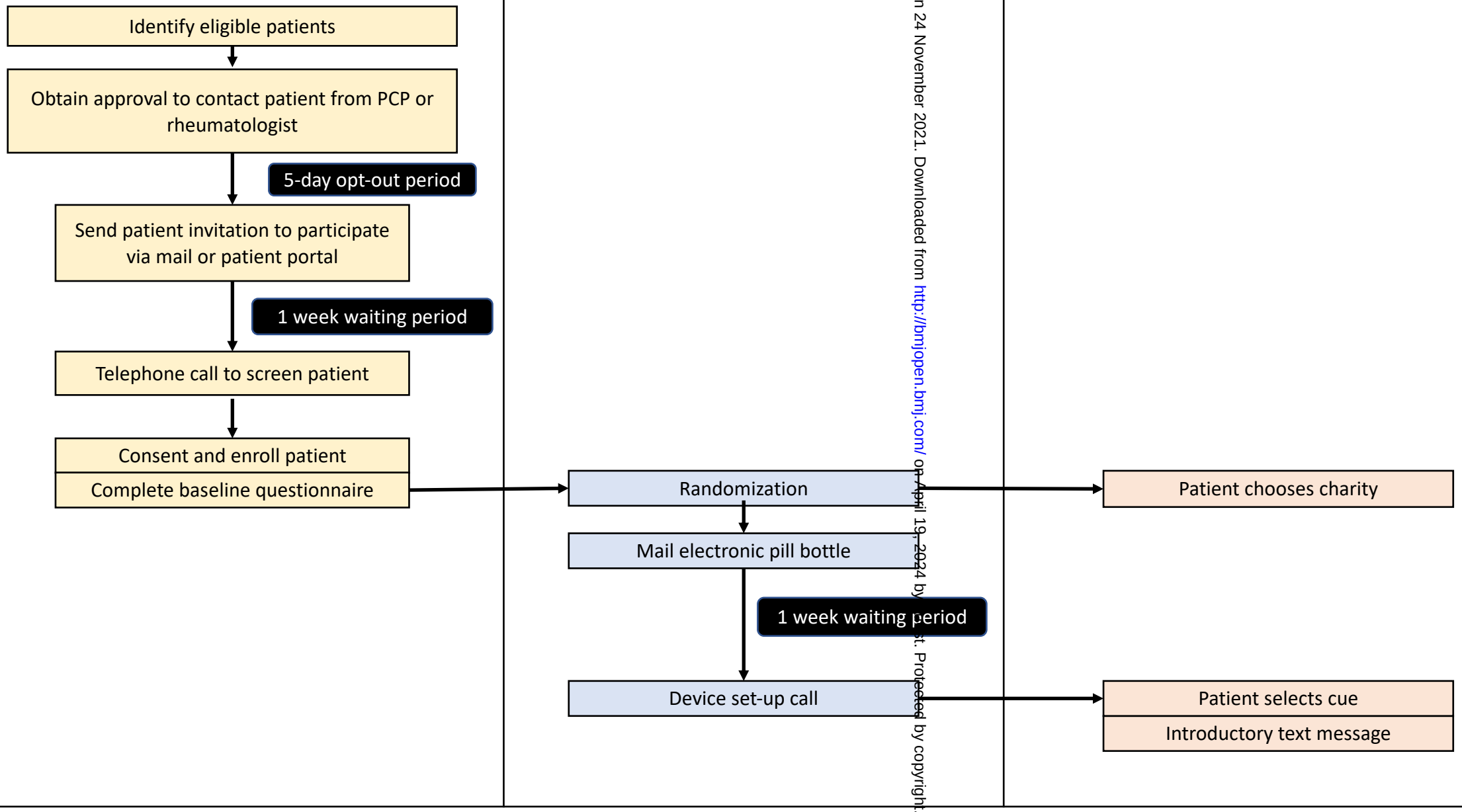
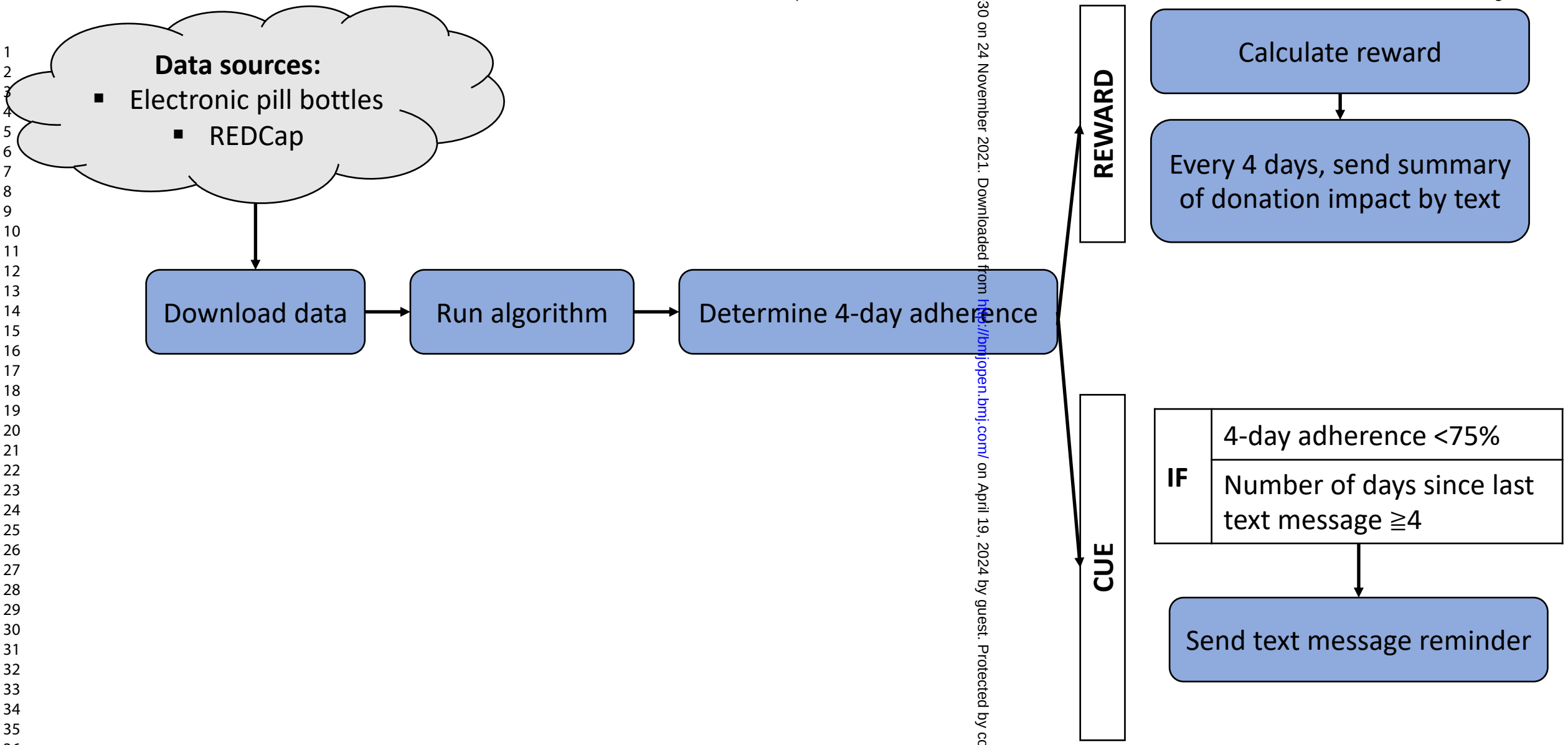
Figure 1. Trial Design

Figure 2. Screening and Recruitment Procedures

Figure 3. Daily Procedures







INSTRUCTIONS FOR USING YOUR PILL BOTTLE

This electronic pill bottle is **the same as your regular pill bottle,** but the cap records when you open and close the bottle. Over the next 6 months, we will use the bottle to measure when you take your medication. In order to set up the bottle, **please follow the instructions below:**

☐ **Place your pills into the provided vials and place the appropriate cap on the vial.** You should only use the electronic cap for study medications:

- [Medication 1]
- [Medication 2]

☐ **Download the Pillsy mobile application from the Apple Store or Android App Store.** By searching "Pillsy" you will be able to find it. Make sure you enable push notifications so you will know if there is a connectivity issue between the application and the bottle.

Please contact us at [RA phone number] or email me at [RA email]

STOP HERE – CALL US TO SET UP THE BOTTLE

☐ **Give us a call to finalize the bottle set up.** Once you complete the steps above, you will be asked for a security code. The security code is sent to one of our study phones, and as such we will need to have a quick conversation on the phone to help you set up the bottle. **We will give you a call a few days after mailing the bottle, but please feel free to contact us once you receive it.**

☐ **Make the pill bottle part of your daily routine.** The questions below will help you decide where to place your pill bottle and remember to use it as part of your routine.

INSTRUCTIONS FOR USING YOUR PILL BOTTLE

People have different ways of taking their medications daily. **What do you tend to do most of the time?**

I take my [*medication*] at ____ AM/PM

What do you also do around the same time? Could you use that activity as a reminder to take your medication?

You can choose an activity from one of the examples below or come up with your own.

EXAMPLES		
		
Getting dressed Making coffee/tea _____	Eating lunch Leaving from work _____	Reading before bed Brushing your teeth _____

I will now take my medication when I… _____

In the blanks below, write down how you will remember that it's time to take your medication.

EXAMPLE	
To remember to take my medication when I *make my morning tea*	**I will** *place my pill bottle near the kettle*
MY COMMITMENT	
To remember to take my medication when **I** _____	**I will** _____ _____

So, as you go about your regular routine, **you will now also think to yourself, "time to take my medication!"**

Cue Text Messages

Text ID	Timeline	Adherence measured over	Text Message
0	Day 0	NA	Hi from Brigham and Women's Hospital's medication study! As a reminder, you planned to take your medication when [cue]. [1/2] If you haven't put your medications near your [cue location], now may be a good time. [2/2]
1	Day + 4 or first time patient's 4-day adherence falls under 75%	4 days	When you [cue], remember to take your medication.
2	Text 1 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
3	Text 2 + 4 days with PDC ≤75%	4 days	You put your medication [location] as a reminder to take them. Is there another activity that would be a better reminder for you? If so, let us know.
4	Text 3 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
5	Text 4 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
6	Text 5 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
7	Text 6 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
8	Text 7 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
9	Text 8 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
10	Text 9 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
11	Text 10 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
12	Text 11 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
13	Text 12 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
14	Text 13 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.

15	Text 14 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
16	Text 15 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
17	Text 16 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
18	Text 17 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
19	Text 18 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
20	Text 19 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
21	Text 20 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
22	Text 21 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
23	Text 22 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.

Charity Sticker

- **Greater Boston Food Bank**

- **Animal Rescue League**

- **UNICEF**

Reward Text Messages

Initial sample message: Welcome! Each time you take your medications this week, a donation will be made to _____ to help [mission].

Follow-up messages: By taking your medication, you helped [mission]. Thanks to you, [charity] will be able to [X]

- By taking your medication, you helped take care of animals. Thanks to you, the Animal Rescue League has been able to feed a homeless dog for 2 days.
- By taking your medication, you helped people struggling with hunger. Thanks to you, the Greater Boston Area Food Bank has been able to prepare 8 free meals.
- By taking your medication, you helped improve children's health. Thanks to you, UNICEF has been able to provide a family with 1 week of clean water.

Reward by PDC:

PDC	Animal Rescue League	Food bank	UNICEF
0%	Feed a homeless dog for 0 days.	Prepare 0 free meals.	Provide a family with 0 days of clean water.
12.5%	Feed a homeless dog for 1 day	Prepare 1 free meals.	Provide a family with 2 days of clean water.
25%	Feed a homeless dog for 2 days.	Prepare 2 free meals.	Provide a family with 4 days of clean water.
37.5%	Feed a homeless dog for 3 days	Prepare 3 free meals.	Provide a family with 6 days of clean water.
50%	Feed a homeless dog for 4 days.	Prepare 4 free meals.	Provide a family with 1 week of clean water.
62.5%	Feed a homeless dog for 5 days	Prepare 5 free meals.	Provide a family with 8 days of clean water.
75%	Feed a homeless dog for 6 days.	Prepare 6 free meals.	Provide a family with 10 days of clean water.
87.5%	Feed a homeless dog for 7 days	Prepare 7 free meals.	Provide a family with 12 days of clean water.
100%	Feed a homeless dog for 8 days.	Prepare 8 free meals.	Provide a family with 2 weeks of clean water.

Timepoints at which texts will be received:

Timeline	Animal Rescue League	Food bank	UNICEF
Day + 4	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 8	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 12	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 16	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 20	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 24	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 28	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 32	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 36	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 40	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 44	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 48	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 52	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 56	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 60	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 64	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 68	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 72	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 76	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 80	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 84	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 88	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 92	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.

Reward Text Messages

BASELINE SURVEY

DEMOGRAPHICS

1) How old are you (in years)? _____

2) What is your gender? _____

3) What is your race/ethnicity? (select multiple options if applicable)

- White
- Black or African American
- American Indian/ Alaska Native
- Asian
- Native Hawaiian or Other Pacific Islander
- Hispanic/Latinx

4) What is your education level?

- Less than high school diploma
- High school diploma
- Some college
- College degree
- Graduate degree

5) What is your employment status?

- Employed
- Job seeking
- Not job seeking
- Retired
- Disabled

6) What is your income?

- Less than $20,000
- $20,000 to $34,999
- $35,000 to $49,999
- $50,000 to $74,999

BASELINE SURVEY

- ○ $75,000 to $99,999
- ○ Over $100,000

7) What is your marital status?

- ○ Married
- ○ Living with partner/ Domestic partnership
- ○ Widowed
- ○ Divorced/ Separated
- ○ Never Married/ Single

8) How many medications are you currently taking on a daily basis?

_____

9) How many medications do you take on a weekly or every other week basis? _____

BASELINE SURVEY

DISEASE ACTIVITY

1. **Are you having a gout attack (flare) today?**
   - ○ Yes
   - ○ No

2. **Are any of your joints swollen**?
   - ○ Yes
   - ○ No

3. **Are any of your joints warm to touch?**
   - ○ Yes
   - ○ No

4. **Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the level of pain when it was at its worst:**

○	○	○	○	○	○	○	○	○	○
1	2	3	4	5	6	7	8	9	10

BASELINE SURVEY

MEDICATION USE

We have printed out your medication list. Please circle the medications your doctor has prescribed for at least 4 months.

_____

_____

Please list the medications your rheumatologist prescribes that you take at least once a day.

_____

_____

Please answer the following questions about your gout medication(s) These questions are about your views on your health and medication(s). There are no right or wrong answers. We are interested in your personal views. All answers will be private and confidential, so please answer honestly.

In the last 30 days, on how many *days* did you miss at least one dose of any of this medication?

1	Write in number of days (0-30):	

		Very poor	Poor	Fair	Good	Very good	Excellent
2	In the last 30 days, how good a job did you do at taking your medication(s) in the way you were supposed to?	○	○	○	○	○	○

BASELINE SURVEY

		Never	Rarely	Sometimes	Usually	Almost always	Always
3	In the last 30 days, how often did you take your medication(s) in the way you were supposed to?	○	○	○	○	○	○

Please rate each statement from 1(not at all) to 7 (very much so) by circling the number you think most closely aligns with your opinion.

		1 (Not at all)	2	3	4	5	6	7 (Very much so)
4	Taking my medication(s) is part of a routine I have	○	○	○	○	○	○	○
5	I typically take my medication(s) at the same time of the day	○	○	○	○	○	○	○
6	I take my medication(s) a certain way and will continue to do so this way in the future	○	○	○	○	○	○	○
6b	When I take my medications, it's usually in the same place (e.g., bathroom, kitchen).	○	○	○	○	○	○	○
6c	When taking my medications, there's something I typically do right before (e.g., brush teeth, sit down at the table)?	○	○	○	○	○	○	○
6d	I usually drink water when I take my medications.	○	○	○	○	○	○	○
6e	I have a cup/ glass I typically use when I take my medications.	○	○	○	○	○	○	○
6f	I usually keep all of my medications in the same place in my home.	○	○	○	○	○	○	○

BASELINE SURVEY

Please answer whether each statement is true about you by circling YES or NO.

Taking my daily medication is something….

7. I do automatically …….. YES NO
8. I do without having to consciously remember …….. YES NO
9. I do without thinking …….. YES NO
10. I start doing before I realize I'm doing it …….. YES NO

Please mark one circle in each row to show how much you agree or disagree with the statement.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
11	Coming regularly to my clinic appointments is good for my health.	○	○	○	○	○
12	My treatment plan for arthritis/lupus/gout will make a big difference in keeping my rheumatic condition under control.	○	○	○	○	○
13	Medications help to control arthritis/lupus/gout	○	○	○	○	○
14	If medications are prescribed, it's important to take the medications every day to control rheumatic disease	○	○	○	○	○
15	Not taking medications every day affects how well the arthritis/lupus/gout treatment works	○	○	○	○	○
16	An arthritis/lupus/gout patient who is feeling well can safely stop taking rheumatic medications	○	○	○	○	○
17	An arthritis/lupus/gout patient who follows recommended care for arthritis/lupus/gout can expect to live long	○	○	○	○	○
18	There is a lot I can do to control my arthritis/lupus/gout	○	○	○	○	○
19	What I do can determine whether my arthritis/lupus/gout gets better or worse	○	○	○	○	○
20	My actions will have no effect on the outcome of my arthritis/lupus/gout	○	○	○	○	○

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	Trial Protocol
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	8-10
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A Randomized Controlled Trial Targeting Habit Formation to Improve Medication Adherence to Daily Oral Medications in Patients with Gout

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Primary Subject Heading:	Rheumatology
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A RANDOMIZED 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 3-arm parallel randomized controlled trial tests an adaptive intervention that leverages the repetition cue-reward principle. The trial will begin recruitment in July 2021 in Boston, MA. 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 randomized 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 $0.50 per day of medication taken. Arm 2 will be adaptive; participants will receive a $0.25 per adherent-day and no reminder texts. If their adherence is <75% 6 weeks post-randomization, their reward will increase to $0.50 per adherent-day and they wil receive reminder texts. The primary outcome is adherence to gout medications over 18 weeks.

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

Registration details: clinicaltrials.gov(NCT04776161)

ARTICLE SUMMARY

Strengths and limitations

- The study uses a randomized 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 personalized 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.

INTRODUCTION

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

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

One promising strategy to increase medication adherence in significant and sustainable ways is approaching medication-taking as a daily habit.[4] Taking a medication every day is similar to other repetitive behaviors 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.[10, 11] The repetition-cue-reward model proposes that habit formation has three central components: behavioral repetition, associated context cues and rewards.[12, 13] 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 behavior rather

than intention[13]. For example, eating habits are stronger determinants of food choices than eating intentions or susceptibility to eating temptations.[14]

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 randomized 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 randomized controlled trial designed to evaluate a habit formation intervention for improving adherence to daily ULT among individuals with gout (see Figure 1). The trial is funded by the National Institute on Aging and is registered on ClinicalTrials.gov (NCT0477616). Enrollment will begin in July 2021 and we plan to complete follow-up by April 2022.

Study Setting and participants

We will enroll 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 center in Boston, MA caring for over 4,000 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. for list of eligible oral medications), 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.

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 through 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 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 the REDCap electronic data capture tool. [15, 16] This paperless consent process was approved by our Institutional Review Board (IRB). At the end of the enrollment visit, they will be randomized to one of 3 arms. All participants will then be mailed up to 2 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 **Supplement 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.

Randomization

Study enrollment will begin in July 2021 and is anticipated to be completed by December 2021. In order to improve balance between the 3 arms, we will use block randomization 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 randomized by research assistants in a 1:1:1 ratio within blocks of 3 participants to one of 3 treatment arms using the randomization module integrated in the REDCap electronic data capture platform.[15, 16]

Interventions

This trial will have 2 intervention arms and 1 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 to which activity each individual wants to link their medication-taking (see **Supplement 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 assited 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 **Supplement 2**).

The 'reward' will consist of a charitable donation every time the participant takes their medication. Participants will choose a charity during the enrollment visit, in specific a local animal shelter, a local food bank, and UNICEF. To make the reward more proximal 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 **Supplement 3**). Every day that the participant takes their medication as prescribed, $0.50 will be donated to their charity of choice. Participants will receive texts every 4 days summarizing how much money was donated on their behalf and the potential impact of their donation (see **Supplement 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 8 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 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 $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 **Supplement 4**). They will receive these text messages over the following 6 weeks. Additionally, non-adherent participants will also see their charity reward increased to $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 Supplement 5**). Additionally they will complete the Self-Report Behavior Automaticity Index (SBRAI),[17] which assesses whether participants complete a given activity (such as medication-taking) automatically, for example by asking if they start doing it before they realize they are doing it. We will also use the routine assessment questionnaire developed by Heintzelman et al[18], 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.[19] Coexisting medical conditions and uric acid values will be extracted from the patient's electronic health record. 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 USD50 gift card upon 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.[20] Despite this, monitoring does have theoretical potential to influence adherence itself. To minimize 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[21], as has been observed in other medication adherence studies.[22, 23] 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 randomization. We will use an average of averages approach [24], 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[25, 26] and will consider the results of this analysis exploratory.

Statistical analysis, sample size and power estimates

We will include all patients randomized 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 X^2 tests and their non-parametric analogues, as appropriate.

The outcomes will be evaluated using intention-to-treat principles among all randomized participants. Change in mean adherence and mean uric acid level will be analyzed using generalized 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 post-randomization lab values available and using multiple imputation.[27]

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 randomizing 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 analyzed with SAS 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 behavior 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 randomized controlled trial of a low-intensity habit formation intervention for weight

control led to increased weight loss maintained over time.[28] We hypothesize 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 enroll patients who have access to a cell phone. While cell phone usage is almost ubiquitous in the United States[29], there are still individuals without one who would not be able to participate, which may limit the generalizability 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 effect 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 suggests suboptimal ULT use. Randomization 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 behaviors.

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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AUTHORS' CONTRIBUTIONS

All authors meet International Committee of Medical Journal Editors (ICMJE) criteria. CPF contributed meaningfully to trial or intervention design and implementation and drafted the trial protocol and manuscript. CHF had overall responsibility for the trial design and helped draft the trial protocol and manuscript. NKC is the co-principal investigator, had overall responsibility for the trial design and trial protocol, and helped draft the trial protocol and manuscript. WW, TR, NH, RO, ESS, EK, KH, RAB, and JCL contributed meaningfully to trial or intervention design and implementation as well as the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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COMPETING INTERESTS

Dr. Feldman serves in unpaid positions on the Board of Directors of the American College of Rheumatology and on the Medical-Scientific Advisory Council of the Lupus Foundation of America. She receives research support from Pfizer Pharmaceuticals unrelated to this work. Dr. Choudhry is a consultant to and holds equity in RxAnte, unrelated to this work. He receives grant funding, payable to his institution, from Boehringer Ingelheim and Humana, also unrelated to the current work. Dr. Barlev is funded by an unrestricted educational grant from Boehringer Ingelheim to the Brigham and Women's Hospital, unrelated to the current work.

DATA SHARING STATEMENT

Data will be available upon reasonable request, pending appropriate agreements and Institutional Review Board approval, including patient data and programming code.

PATIENT CONSENT FOR PUBLICATION

Not required

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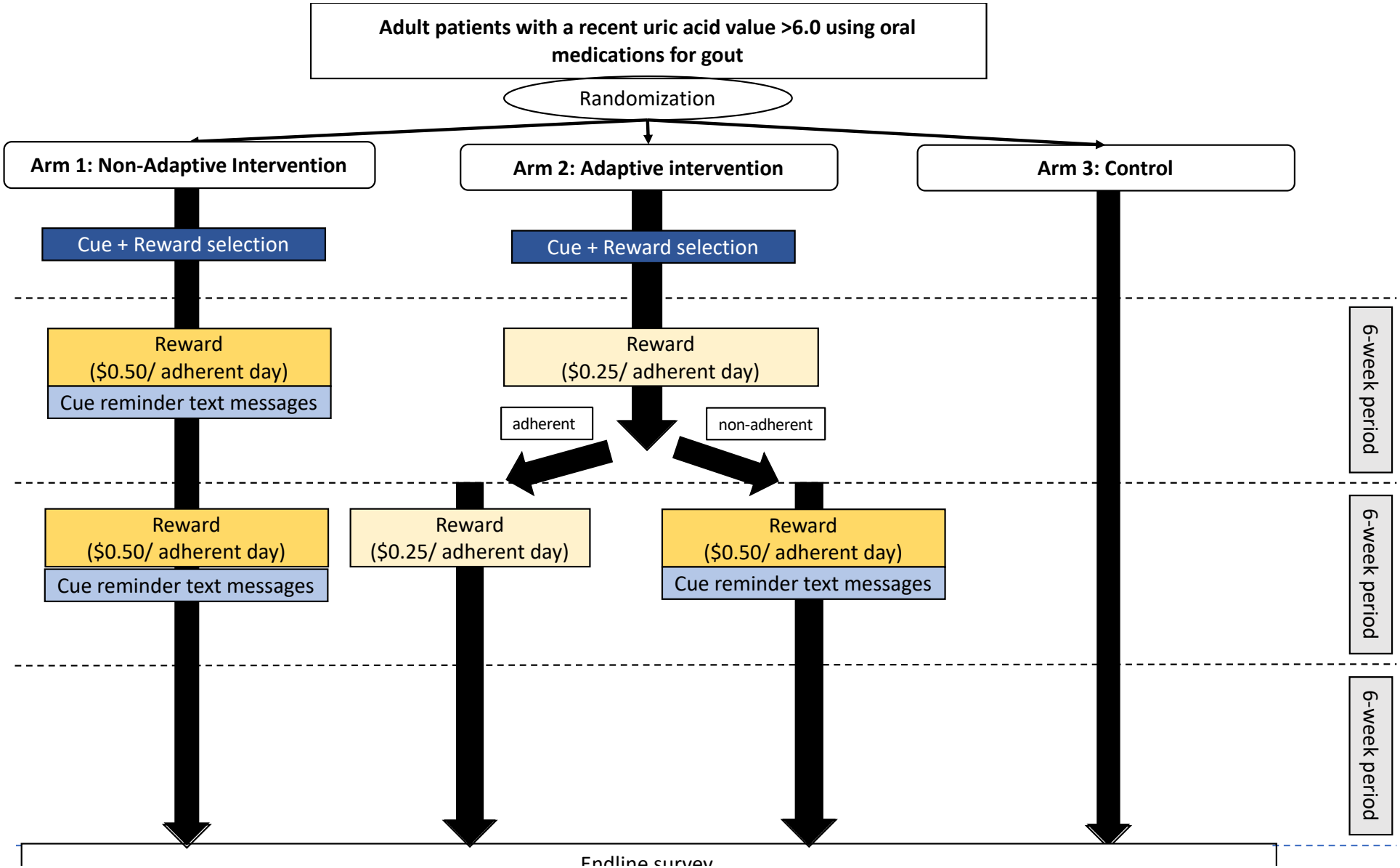
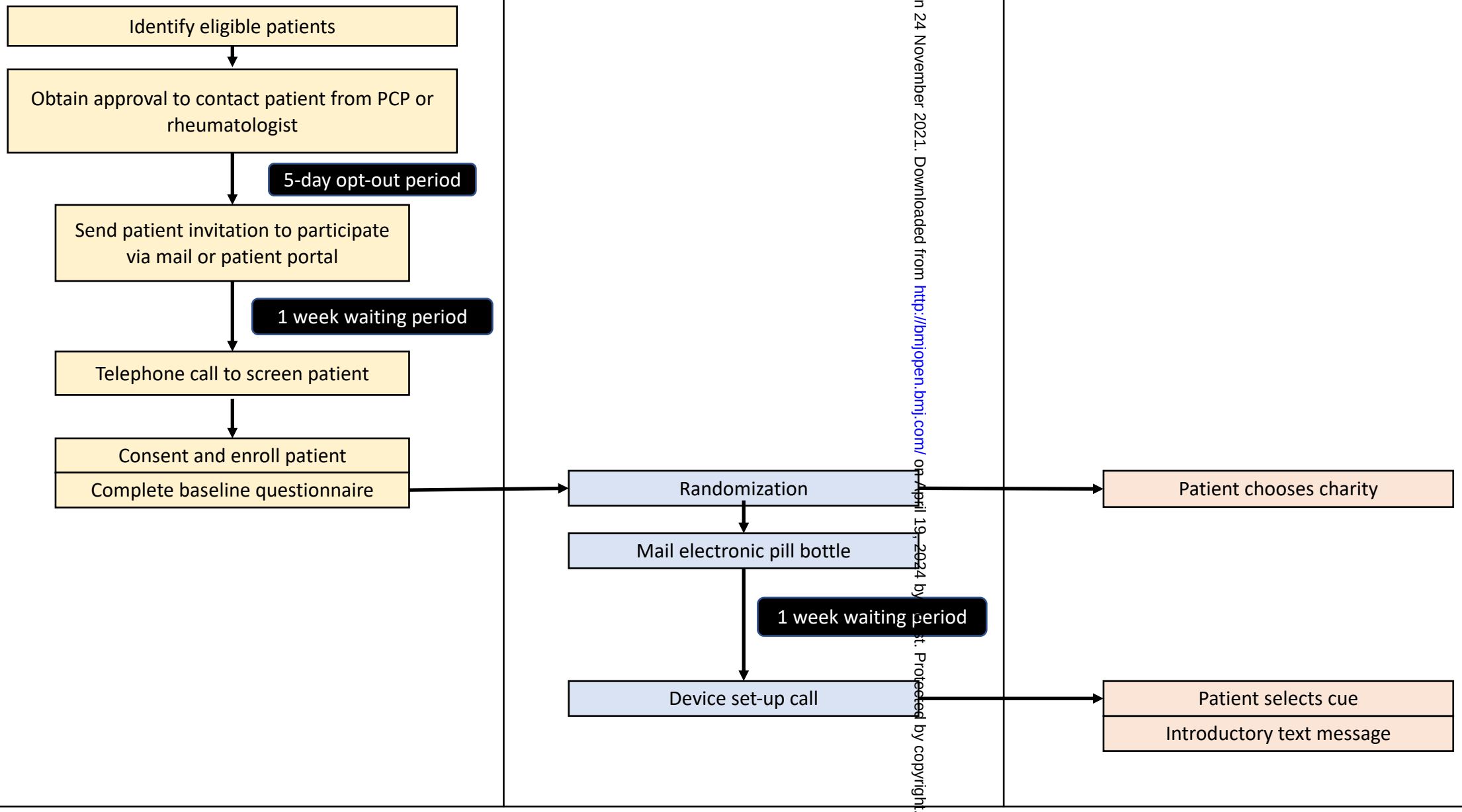
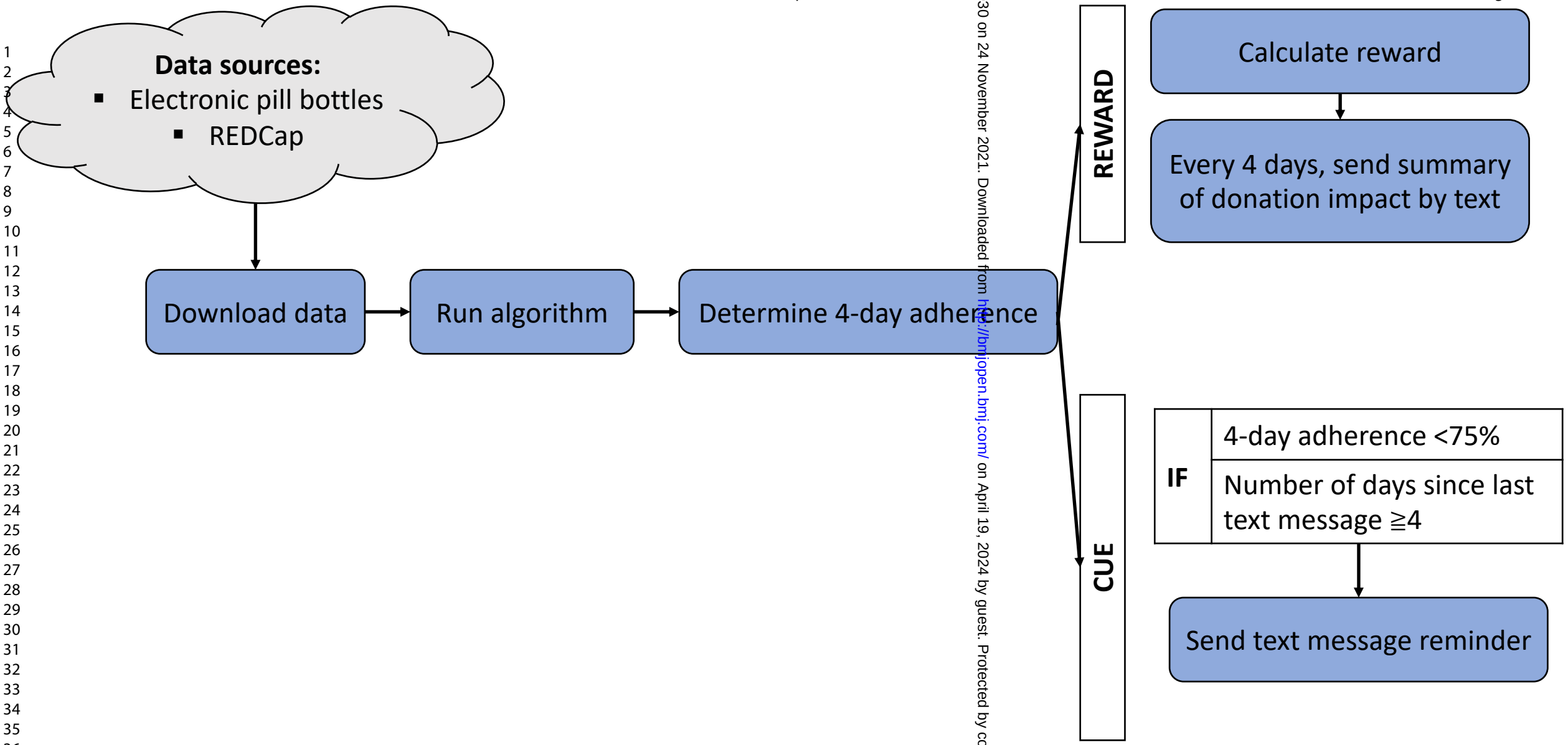
Figure 1. Trial Design

Figure 2. Screening and Recruitment Procedures

Figure 3. Daily Procedures







INSTRUCTIONS FOR USING YOUR PILL BOTTLE

This electronic pill bottle is **the same as your regular pill bottle,** but the cap records when you open and close the bottle. Over the next 6 months, we will use the bottle to measure when you take your medication. In order to set up the bottle, **please follow the instructions below:**

☐ **Place your pills into the provided vials and place the appropriate cap on the vial.** You should only use the electronic cap for study medications:

- [Medication 1]
- [Medication 2]

☐ **Download the Pillsy mobile application from the Apple Store or Android App Store.** By searching "Pillsy" you will be able to find it. Make sure you enable push notifications so you will know if there is a connectivity issue between the application and the bottle.

Please contact us at [RA phone number] or email me at [RA email]

STOP HERE – CALL US TO SET UP THE BOTTLE

☐ **Give us a call to finalize the bottle set up.** Once you complete the steps above, you will be asked for a security code. The security code is sent to one of our study phones, and as such we will need to have a quick conversation on the phone to help you set up the bottle. **We will give you a call a few days after mailing the bottle, but please feel free to contact us once you receive it.**

☐ **Make the pill bottle part of your daily routine.** The questions below will help you decide where to place your pill bottle and remember to use it as part of your routine.

INSTRUCTIONS FOR USING YOUR PILL BOTTLE

People have different ways of taking their medications daily. **What do you tend to do most of the time?**

I take my [*medication*] at ____ AM/PM

What do you also do around the same time? Could you use that activity as a reminder to take your medication?

You can choose an activity from one of the examples below or come up with your own.

EXAMPLES		
		
Getting dressed Making coffee/tea _____	Eating lunch Leaving from work _____	Reading before bed Brushing your teeth _____

I will now take my medication when I… _____

In the blanks below, write down how you will remember that it's time to take your medication.

EXAMPLE	
To remember to take my medication when I *make my morning tea*	**I will** *place my pill bottle near the kettle*
MY COMMITMENT	
To remember to take my medication when **I** _____	**I will** _____ _____

So, as you go about your regular routine, **you will now also think to yourself, "time to take my medication!"**

Cue Text Messages

Text ID	Timeline	Adherence measured over	Text Message
0	Day 0	NA	Hi from Brigham and Women's Hospital's medication study! As a reminder, you planned to take your medication when [cue]. [1/2] If you haven't put your medications near your [cue location], now may be a good time. [2/2]
1	Day + 4 or first time patient's 4-day adherence falls under 75%	4 days	When you [cue], remember to take your medication.
2	Text 1 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
3	Text 2 + 4 days with PDC ≤75%	4 days	You put your medication [location] as a reminder to take them. Is there another activity that would be a better reminder for you? If so, let us know.
4	Text 3 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
5	Text 4 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
6	Text 5 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
7	Text 6 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
8	Text 7 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
9	Text 8 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
10	Text 9 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
11	Text 10 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
12	Text 11 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
13	Text 12 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
14	Text 13 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.

15	Text 14 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
16	Text 15 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
17	Text 16 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
18	Text 17 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
19	Text 18 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
20	Text 19 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.
21	Text 20 + 4 days with PDC ≤75%	4 days	You put your medication [location]. Don't forget to take them when you [cue].
22	Text 21 + 4 days with PDC ≤75%	4 days	Remember to take your medication when you are [same cue or new cue].
23	Text 22 + 4 days with PDC ≤75%	4 days	When you [cue], remember to take your medication.

Charity Sticker

- **Greater Boston Food Bank**

- **Animal Rescue League**

- **UNICEF**

Reward Text Messages

Initial sample message: Welcome! Each time you take your medications this week, a donation will be made to _____ to help [mission].

Follow-up messages: By taking your medication, you helped [mission]. Thanks to you, [charity] will be able to [X]

- By taking your medication, you helped take care of animals. Thanks to you, the Animal Rescue League has been able to feed a homeless dog for 2 days.
- By taking your medication, you helped people struggling with hunger. Thanks to you, the Greater Boston Area Food Bank has been able to prepare 8 free meals.
- By taking your medication, you helped improve children's health. Thanks to you, UNICEF has been able to provide a family with 1 week of clean water.

Reward by PDC:

PDC	Animal Rescue League	Food bank	UNICEF
0%	Feed a homeless dog for 0 days.	Prepare 0 free meals.	Provide a family with 0 days of clean water.
12.5%	Feed a homeless dog for 1 day	Prepare 1 free meals.	Provide a family with 2 days of clean water.
25%	Feed a homeless dog for 2 days.	Prepare 2 free meals.	Provide a family with 4 days of clean water.
37.5%	Feed a homeless dog for 3 days	Prepare 3 free meals.	Provide a family with 6 days of clean water.
50%	Feed a homeless dog for 4 days.	Prepare 4 free meals.	Provide a family with 1 week of clean water.
62.5%	Feed a homeless dog for 5 days	Prepare 5 free meals.	Provide a family with 8 days of clean water.
75%	Feed a homeless dog for 6 days.	Prepare 6 free meals.	Provide a family with 10 days of clean water.
87.5%	Feed a homeless dog for 7 days	Prepare 7 free meals.	Provide a family with 12 days of clean water.
100%	Feed a homeless dog for 8 days.	Prepare 8 free meals.	Provide a family with 2 weeks of clean water.

Timepoints at which texts will be received:

Timeline	Animal Rescue League	Food bank	UNICEF
Day + 4	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 8	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 12	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 16	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 20	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 24	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 28	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 32	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 36	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 40	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 44	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 48	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 52	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 56	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 60	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 64	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 68	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 72	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 76	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 80	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 84	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 88	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.
Day + 92	Feed a homeless dog for [0-8] days.	Prepare [0-8] free meals.	a family with [0-2] weeks of clean water.

Reward Text Messages

BASELINE SURVEY

DEMOGRAPHICS

1) How old are you (in years)? _____

2) What is your gender? _____

3) What is your race/ethnicity? (select multiple options if applicable)

- White
- Black or African American
- American Indian/ Alaska Native
- Asian
- Native Hawaiian or Other Pacific Islander
- Hispanic/Latinx

4) What is your education level?

- Less than high school diploma
- High school diploma
- Some college
- College degree
- Graduate degree

5) What is your employment status?

- Employed
- Job seeking
- Not job seeking
- Retired
- Disabled

6) What is your income?

- Less than $20,000
- $20,000 to $34,999
- $35,000 to $49,999
- $50,000 to $74,999

BASELINE SURVEY

- ○ $75,000 to $99,999
- ○ Over $100,000

7) What is your marital status?

- ○ Married
- ○ Living with partner/ Domestic partnership
- ○ Widowed
- ○ Divorced/ Separated
- ○ Never Married/ Single

8) How many medications are you currently taking on a daily basis?

_____

9) How many medications do you take on a weekly or every other week basis? _____

BASELINE SURVEY

DISEASE ACTIVITY

1. **Are you having a gout attack (flare) today?**
   - ○ Yes
   - ○ No

2. **Are any of your joints swollen**?
   - ○ Yes
   - ○ No

3. **Are any of your joints warm to touch?**
   - ○ Yes
   - ○ No

4. **Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the level of pain when it was at its worst:**

○	○	○	○	○	○	○	○	○	○
1	2	3	4	5	6	7	8	9	10

BASELINE SURVEY

MEDICATION USE

We have printed out your medication list. Please circle the medications your doctor has prescribed for at least 4 months.

_____

_____

Please list the medications your rheumatologist prescribes that you take at least once a day.

_____

_____

Please answer the following questions about your gout medication(s) These questions are about your views on your health and medication(s). There are no right or wrong answers. We are interested in your personal views. All answers will be private and confidential, so please answer honestly.

In the last 30 days, on how many *days* did you miss at least one dose of any of this medication?

1	Write in number of days (0-30):	

		Very poor	Poor	Fair	Good	Very good	Excellent
2	In the last 30 days, how good a job did you do at taking your medication(s) in the way you were supposed to?	○	○	○	○	○	○

BASELINE SURVEY

		Never	Rarely	Sometimes	Usually	Almost always	Always
3	In the last 30 days, how often did you take your medication(s) in the way you were supposed to?	○	○	○	○	○	○

Please rate each statement from 1(not at all) to 7 (very much so) by circling the number you think most closely aligns with your opinion.

		1 (Not at all)	2	3	4	5	6	7 (Very much so)
4	Taking my medication(s) is part of a routine I have	○	○	○	○	○	○	○
5	I typically take my medication(s) at the same time of the day	○	○	○	○	○	○	○
6	I take my medication(s) a certain way and will continue to do so this way in the future	○	○	○	○	○	○	○
6b	When I take my medications, it's usually in the same place (e.g., bathroom, kitchen).	○	○	○	○	○	○	○
6c	When taking my medications, there's something I typically do right before (e.g., brush teeth, sit down at the table)?	○	○	○	○	○	○	○
6d	I usually drink water when I take my medications.	○	○	○	○	○	○	○
6e	I have a cup/ glass I typically use when I take my medications.	○	○	○	○	○	○	○
6f	I usually keep all of my medications in the same place in my home.	○	○	○	○	○	○	○

BASELINE SURVEY

Please answer whether each statement is true about you by circling YES or NO.

Taking my daily medication is something….

7. I do automatically …….. YES NO
8. I do without having to consciously remember …….. YES NO
9. I do without thinking …….. YES NO
10. I start doing before I realize I'm doing it …….. YES NO

Please mark one circle in each row to show how much you agree or disagree with the statement.

		Strongly disagree	Disagree	Neutral	Agree	Strongly agree
11	Coming regularly to my clinic appointments is good for my health.	○	○	○	○	○
12	My treatment plan for arthritis/lupus/gout will make a big difference in keeping my rheumatic condition under control.	○	○	○	○	○
13	Medications help to control arthritis/lupus/gout	○	○	○	○	○
14	If medications are prescribed, it's important to take the medications every day to control rheumatic disease	○	○	○	○	○
15	Not taking medications every day affects how well the arthritis/lupus/gout treatment works	○	○	○	○	○
16	An arthritis/lupus/gout patient who is feeling well can safely stop taking rheumatic medications	○	○	○	○	○
17	An arthritis/lupus/gout patient who follows recommended care for arthritis/lupus/gout can expect to live long	○	○	○	○	○
18	There is a lot I can do to control my arthritis/lupus/gout	○	○	○	○	○
19	What I do can determine whether my arthritis/lupus/gout gets better or worse	○	○	○	○	○
20	My actions will have no effect on the outcome of my arthritis/lupus/gout	○	○	○	○	○

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	Trial Protocol
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	8-10
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.