

Novel Methods for Ascertainment of Gout Flares - A Pilot Study

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Summary

Title: Novel Methods for Ascertainment of Gout Flares – A Pilot Study

Duration: 18 months

Study Site(s): University of Alabama at Birmingham (UAB) and University of Nebraska Medical Center (UNMC)

Investigators: Kenneth G. Saag, MD, MSc; Jeffrey Curtis, MD, MPH, MSPH; James Willig, MD, PhD

Methodology: The study is a prospective, randomized, comparison of interactive voice response (IVR) telephone questionnaire/flare reporting system versus RheumPRO (a smartphone study application) with crossover. Adults 18 years and older with gout will be enrolled based on eligibility. Following consent/enrollment individuals will be randomized to either start using an interactive voice response telephone or RheumPRO weekly to track their gout flare status for a period of 12 weeks—Phase 1. At the conclusion of 12 weeks individuals will “crossover” to the opposite study arm and continue for 12 weeks using the opposite mode to report their flare frequency/intensity (i.e., those randomized to IVR for the first phase will use the RheumPRO application in the second phase and vice-versa).

List Abbreviations, Tables, and Figures

Abbreviations :

IVR (Interactive Voice Response)

UAB (University of Alabama at Birmingham)

UNMC (University of Nebraska Medical Center)

Tables:

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1. Study Overview

1.1 A. Background

Acute gout flares are a major cause of morbidity. Flares lead to substantial reductions in health-related quality of life, increased work absenteeism, productivity loss, and substantial healthcare costs. For instance, our group has shown that gout, likely related to acute flares, leads to more than 174,000 emergency department visits in the U.S. annually with corresponding charges approaching \$166 million (1).

In recent surveys conducted by our group, gout patients and healthcare providers alike identified the reduction of gout flares as the highest priority outcome that should be examined in future comparative effectiveness studies of urate lowering therapy (ULT) (unpublished results). Despite consensus about the importance of capturing flares, clinical trials investigating ULTs (2-6) or anti-inflammatory prophylaxis (7) have used inconsistent flare definitions and methods of flare ascertainment. The inconsistency has likely been driven by the absence of a standardized definition or ascertainment method. These deficits limit comparisons that can be made across investigations.

Recently, a group supported by the American College of Rheumatology & European League Against Rheumatism (ACR & EULAR) has attempted to define a gout flare (8-10). For simplicity, the group focused on defining only those flares occurring after a definitive gout diagnosis. Nine elements of a flare definition emerged from the first two studies (8, 9). These nine elements included physician reported information, laboratory data and patient self-report. In a third study, Gaffo et al. compared the discriminatory ability of the self-reported items against the gold standard of a rheumatologist's judgment of flare presence (10). Self-report of 4 criteria had the greatest discriminatory ability with an area under the curve (AUC) of 0.931 (10). These promising results indicate the important role for a standardized self-report definition of a gout flare.

In addition to variability in gout flare definitions, the optimal method for obtaining self-reported flares remains undefined. An early study of febuxostat, for example, assessed flares weekly at physician visits (2). Another study counted a flare only when it was treated by a healthcare provider (4). Still other studies assessed flares during physician visits occurring at variable time points (3, 6). These inconsistent methods also pose practical limitations given by their time and resource intensive nature. Opportunities to increase efficiency have only recently become available with the validation of the self-reported definition for gout flares described above. Self-report can now be combined with technological advances in remote data collection to develop novel and highly efficient methods to identify gout flares. This study will address a pressing need by leveraging technological advances that facilitate the remote and real-time collection of patient reported outcomes (PROs) in gout.

2 Study Organization and Responsibilities

2.1 Study Roster

Name	Role	Address	Phone #	Email
Kenneth G. Saag, MD, MSc	PI	University of Alabama at Birmingham Division of Clinical Immunology and Rheumatology, FOT 820, Birmingham, AL, 35294	205-996-9784	ksaag@uabmc.edu
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Joshua A. Melnick, MPH	Program Administrator	UAB Division of Clinical Immunology and Rheumatology, FOT 820, Birmingham, AL, 35294	(205) 975-0583	jmelnick@uabmc.edu
Stephanie Biggers, RN	Nurse Coordinator	UAB Division of Clinical Immunology and Rheumatology, FOT 820, Birmingham, AL, 35294	(205) 934-1444	sbiggers@uabmc.edu

2.2 Study Center

Since this is a study, sites will be monitored by the PIs at each respective site (UAB or University of Nebraska Medical Center (UNMC) according to established monitoring standard operating procedures (SOPs). Study site PIs will oversee the study to assure satisfactory data recording, adherence to the study protocol, Good Clinical Practice (GCP), and study medication accounting. UAB and the UNMC will monitor recruitment utilizing automated reports generated from the study database. UAB and UNMC investigators and staff will have meetings bi-weekly to monitor site recruitment and to determine any intervention for poor recruitment. The staff listed in the study roster will be responsible for all aspects of the trial. This includes but is not limited to the following:

- Finalizing the study protocol
- Development of the manual of procedures and its maintenance
- Participant randomization
- Development and implementation of the data flow and data tracking
- Development of procedures for data entry, error identification, and error correction
- AE monitoring and reporting
- Quality control procedures
- Submitting for IRB review and approval
- Creating reports - enrollment, AEs, participant status (e.g., withdrawals)
- Preparing and sending required reports to the Safety Officer and the IRB
- Submitting all required reports to the study appointed Safety Officer.
- Distribution of all changes, updates and policies of above mentioned reports and documents to the study appointed Safety Officer.
- Maintaining the study binder (regulatory and clinical documents)
- Preparation of all study materials- data tables, recruitment materials, official reports
- Identifying, recruiting, screening, and enrolling participants
- Obtaining IC from each participant
- Protecting participants' rights
- Collecting study data and following participants through study completion

- Compliance and accountability of administration of study intervention
- Communicating questions, concerns, and/or observations to the PIs

All of the above activities will be carried out by the study's project coordinators, project managers, and research assistants on a weekly basis (or more frequently as needed) and monitored by the principal and co-investigators.

In the event a problem is identified by either study site PI or staff, a teleconference/webinar will be scheduled to review the issue. These teleconferences/webinars will include discussions of overall recruitment status and identified barriers to recruitment experienced by the site with the study team. Detailed recruitment issues and suggestions will be discussed, as well as identified barriers.

The study will be conducted under the auspices of the IRBs at UAB and the UNMC. Prior to initiation of the study, the investigator will forward copies of the protocol, Investigator's curriculum vitae (if applicable), study advertisements (if applicable), and all other subject-related documents to be used for the study to the IRB for its review and approval. Before initiating a study, the site PI will have written and dated full approval from the responsible IRB for the protocol. The investigators will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

3 Training Plan

Each study staff member will be trained in the protocol by the investigators named above. The investigators and all staff involved in the study will have completed their required IRB / human participants training. New study staff members will be trained on the protocol and spend a visit shadowing another trained staff member before carrying out visits on their own.

Prior to conducting visits, the investigator will be asked to sign off that the staff member has been appropriately trained in the study protocol. Training and delegation of responsibility will be documented in the Study training Log (Tab 4.2) and entered into the study binder.

If a staff performance problem arises, several steps will be taken to resolve the problem. First, the project manager will communicate the problem to the PIs. At this stage, the PIs will work with study personnel to identify causes of the problem and offer solutions. If the problem continues, additional training will be considered. In cases of problems of sufficient severity or intractable problems that are not resolved by the procedures described above, the under-performing team member may be removed from active participation in the study.

4 Communications plan

As this protocol is currently only being carried out at two sites (the UAB and UNMC, meetings will be held between the entire study staff every two weeks to communicate the on-going progress of the study.

Topics of discussion at each meeting will include:

- Recruitment progress
- Technology issues or concerns with the study and possible solutions
- Any data issues to be resolved at that time
- Adverse events Safety reporting
- Other study updates

Additionally, study personnel will keep investigators informed of the weekly progress of the study with weekly study work group meetings and email updates that include the following information:

- Number of patients screened that week
- Number of patient visits overall
- Prospective study participants to speak with the following week
- A recap of any adverse events (which would have already been reported immediately following the event)
- Other study updates
- Any recent data collection that is useful for viewing or necessary to see for safety monitoring

5 Recruitment and Retention Plan

5.1 Recruitment Plan

The target population to be recruited is patients with gout. Patients will be recruited from the UAB gout clinic, The Kirklin Clinic, and the UNMC gout clinic. The inclusion and exclusion criteria will be reviewed (and if the participant wishes to proceed, then informed consent will be obtained by the principal investigator, one of the co-investigators, or a trained member of the study staff. Study procedures will not begin until signed informed consent has been obtained.

5.2 Participant Retention

To encourage adherence to the assigned study arm participants will be contacted 2 weeks after enrollment. Study coordinators will inquire about any challenges encountered (eg. technology issues—Fitbit not syncing, trouble logging in to the IRV/RheumPRO app). In addition, participant progress will be monitored on a weekly basis by UAB to ensure participants are completing their assigned weekly flare surveys. If any data from the participant is missing on the Fitbit, the study team will contact them to ensure they know how to charge their devices and are using it appropriately.

6 Eligibility criteria

No subject will be excluded based upon gender or race/ethnicity. All participants must meet the following criteria to be enrolled:

- \geq to 18 yrs. of age with Current physician diagnosed gout
- current hyperuricemia defined as serum urate level >6.8 mg/dl
 - Or if it has been >3 months since their last urate OR they have had an increase in ULT (or change in medication) in the past 3 months then a new urate of ≥ 6.0 must be documented to satisfy inclusion criteria.
- self-report of at least two gout flares in the previous 6 months

- Current smartphone user utilizing a FitBit compatible smart phone (with the ability to download RheumPRO from web link).

7 Informed Consent and HIPAA

7.1 Overview of the Informed consent document

The process of informed consent will be carried out by one of the study physicians in conjunction with the study coordinator and the research assistant involved in the screening visit after the participant appears to meet the pre-screening criteria. During this process, individuals will be informed of all aspects of the study so that they can make an informed decision. Participants will then confirm their willingness to participate in the research study by signing the Informed Consent form (see Tab 2.2 for the complete informed consent). After the participant has signed the consent form, the Principal Investigator and/or the research coordinator conducting the visit must sign and date the Informed Consent Document.

The informed consent document contains the following:

- Disclosure of relevant information to prospective participants about the research;
- The participant's comprehension of the information;
- The participant's voluntary agreement to participate in a research study without coercion or undue influence.
- Complete disclosure of any appropriate alternative procedures and their risks and benefits
- Disclosure of the extent of confidentiality that will be maintained
- Statement of compensation and/or medical treatment available if injury occurs
- Name, address, and telephone number of the Principal Investigator

By signing the consent form, the participant authorizes the use of their personally identifiable information and personal health information, that they understand the study and its benefits and risks, and agree to all other aspects of the study outlined in the form. Participants can withdraw their consent at any time.

If there is a change in any of the study procedures that may affect the participant, the informed consent document will be revised and approved by the IRB. Any participants enrolled in the study prior to a change in procedures will sign the amended consent form. Per NIH policy, the signed consent forms will be kept as part of the study record for at least 7 years after completion of the study.

Important Steps for the Study Staff:

- Provide participants with adequate information concerning the study procedures and scope
- Provide adequate opportunity for the participant to consider all available options
- Respond to the participant's questions and concerns
- Ensure that each participant understands all information provided
- Obtain the participant's written voluntary consent to participate
- Sign the consent form as witnesses
- Provide participants with a copy of the consent form

- Keep the signed form in the participant's binder

7.2 HIPAA Authorization

The privacy requirements, as outlined by The Health Insurance Portability & Accountability Act (HIPAA) to protect the participant's confidentiality, are met by reading through the consent form with the potential study participant before obtaining a signature. Additionally, the following HIPAA Specific requirements are met in the last section of the consent form:

The form contains language that satisfies the HIPAA requirements and outline the protection of health information utilized in the study. That participants are authorizing investigators, IRBs, research administrators, and others to share and disclose their Protected Health Information (PHI) for research purposes.

8 Study Supplies

Each participant will be supplied with a FitBit Charge HR wearable activity tracker. Fitbit will be supplied by UAB to 45 participants along with study binder.

9 Randomization

Randomization will occur by using a random number generator. Specifically, permuted block randomization will be used for balance between cross-over arms throughout the investigation. The study coordinator will maintain the master list and securely store the randomization files. Upon completion of the informed consent and screening CRFs, the RheumPRO application will automatically create a unique study ID. The study coordinator will initiate the randomization procedure after a subject has consented. If any concerns arise during the randomization procedures, the study coordinator will contact the study statistician.

10 Study Intervention

10.1 Overview

At enrollment a questionnaire will be completed by all participants to capture demographics, gout-specific disease history, type of phone used. If participants meet I/E criteria (see Tab 1.1) they will be offered consent for the study (see Tab 2.2).

RheumPPO is a mobile smartphone application developed by UAB to capture Patient Reported Outcomes and data from electronic health trackers like Fitbit. Installation of RheumPRO is required for all participants to ensure that passive data can be collected from study provided Fitbit (<https://www.fitbit.com/>) that will be provided to all enrolled participants (see below). We are exploring the use of passively collected FitBit data to see if more timely prompts to patients regarding gout flares can be determined. Passively collected data will include: steps, distances, heart rate, floors, minutes at various activity levels, and sleep parameters.

Phase 1:

After consenting to participate in the study participants will be randomized to start with the IVR or RheumPRO intervention (Phase 1) groups. Frequency and questionnaire prompts for each system will be matched.

The IVR system includes tailored scripting of Gout Flare and Patient Reported Outcome questions (with skip logic), recorded by a member of the research team. The system will automatically dial participants at a schedule time (eg. Monday 4 PM) and if no answer will attempt 2 more times at the same time over the following 2 days (eg. Tuesday 4 PM, Wednesday 4 PM). Participants will self-navigate through the questions using their telephone keypad. Participants can also call into the system to complete surveys if they experience a flare on a day they are not scheduled to receive a call. The IVR system will be programmed to call the patient weekly for 12 weeks to complete a weekly Gout Flare Survey. Consistent with the published gout flare self-report definition, gout flare ascertainment questions will include whether the recent flare is similar to past flares, the number of swollen joints and the number of warm joints. Pain at rest during the attack will be assessed on a 0-9 scale. Together, these questions attain 90% accuracy with physician-diagnosed gout. Further questions will include peak pain, timing of attack and duration of attack if completed. We will capture patient reported outcome measures (e.g. pain, fatigue, sleep) using instruments from the NIH PROMIS assessment center (<https://www.assessmentcenter.net/>). In addition IVR questionnaires at months 1, 3, and 6 will assess IVR ease of use, burden of use, willingness to continue use and disruption to daily activities. At enrollment the study coordinator will explain how the IVR works, planned survey schedule, and that participant -initiated calls to IVR are allowed.

Participants randomized in Phase 1 to the RheumPRO application will complete the exact same Gout Flare Survey questions as the participants randomized to the IVR group, but will complete them using the RheumPRO application that will be downloaded on their smartphone. The RheumPRO application will be programmed to notify participants weekly for 26 12 weeks via a scheduled (eg. Monday 4 PM) “pop-up” to complete Gout Flare and Patient Reported Outcomes Surveys. Participants self-navigate through the survey questions using their smartphone. If participants do not complete the Gout Flare RheumPRO will generate 2 more “pop-ups” at the same time over the following 2 days (eg. Tuesday 4 PM, Wednesday 4 PM). Participants can also open the RheumPRO application on their smartphone and complete surveys or if they experience a flare on a day they are not scheduled to complete a survey. In addition, RheumPRO questionnaires at months 1, 3, and 6 will assess RheumPRO ease of use, burden of use, willingness to continue use and disruption to daily activities. At enrollment the study coordinator will explain how RheumPRO works, planned survey schedule, and that participant -initiated surveys in RheumPRO are allowed.

Phase 2:

At the conclusion of 12 weeks individuals will “crossover” to the opposite study arm and will continue in the study for an additional 12 weeks using the opposite technology to report their flare frequency/intensity (i.e., those randomized to IVR for the first phase will use the RheumPRO app in the second phase and vice-versa) completing the exact same Gout Flare and Patient Reported Outcome questions as were completed in Phase 1. Activities to be completed at each study visit are detailed below.

Figure 1. Study Workflow

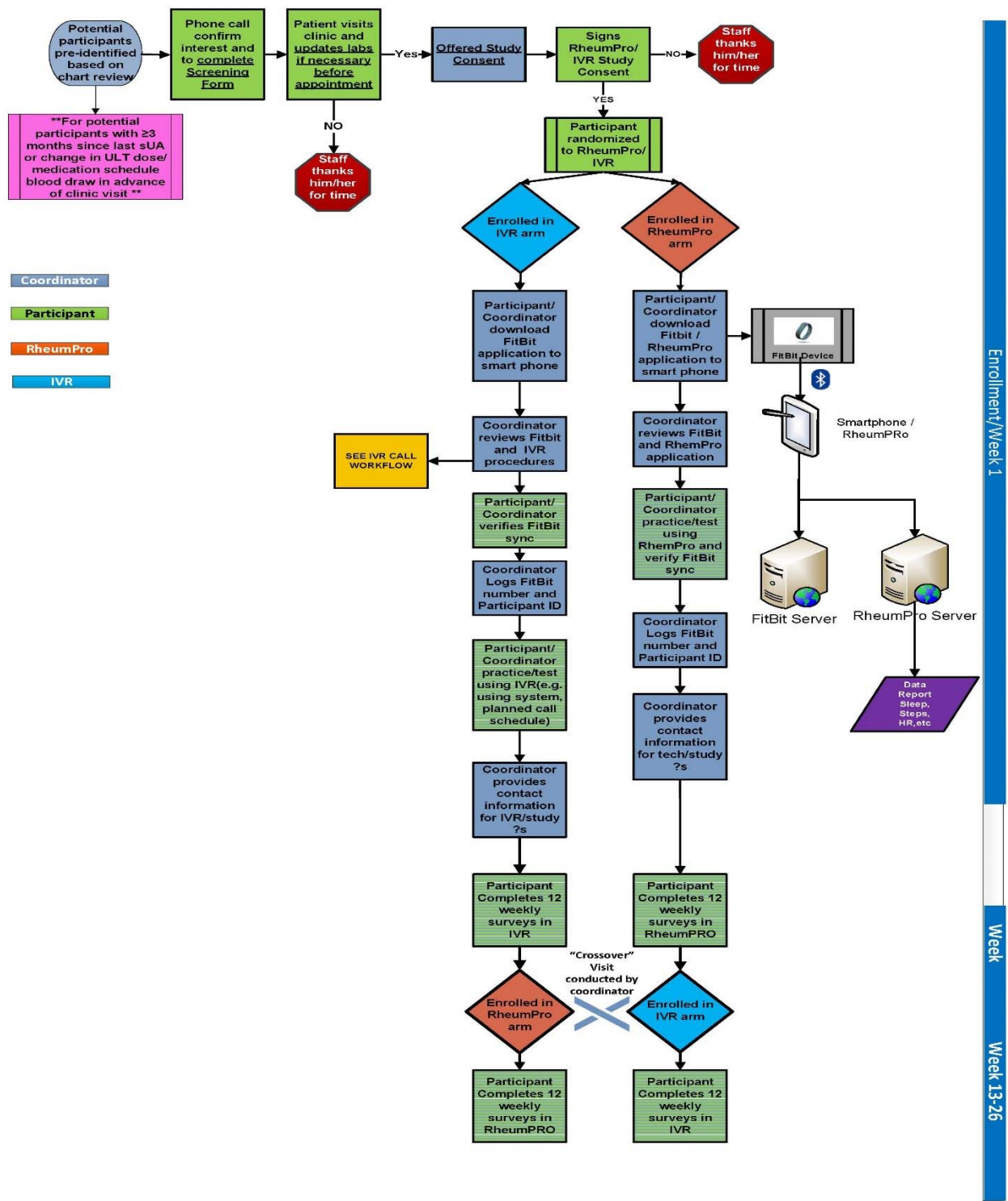


Table 1. Study Visits and Evaluation

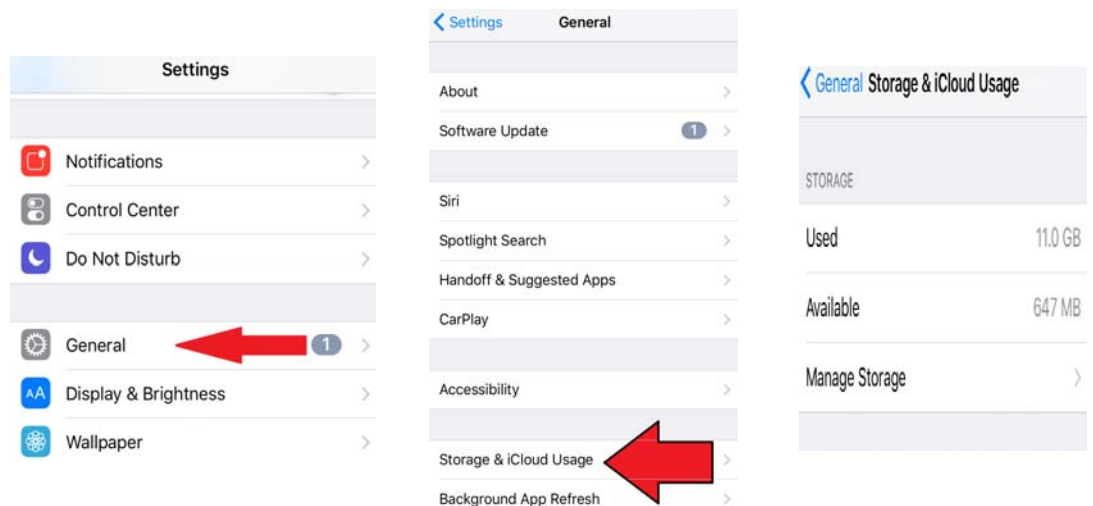
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Informed Consent	X																								
Paper Screening	X																								
Paper Enrollment	X																								
IVR/RheumPRO Initial Flare Assessment	X																								
Patient- Weekly Flare Assessment*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2 week adherence call		X																							
1-month follow-up Assessment and phone check-in				X																					
3-month follow-up Assessment												X													
Crossover Study Visit†													X												
1-month follow-up Assessment and phone check-in																		X							
6-Month follow-up Assessment																									X
Unscheduled Patient Initiated Flare Assessment																									

*Weekly flare assessment are completed by patient using IVR or RheumPRO application; †Crossover visit will be conducted in person at the study site.

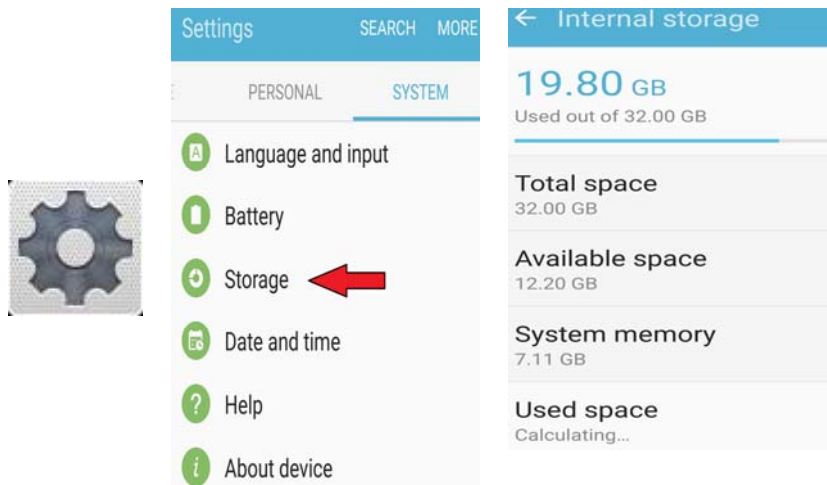
10.2 Participant Evaluations- Study timeline, visits, and procedures

10.2.1 Visit 1

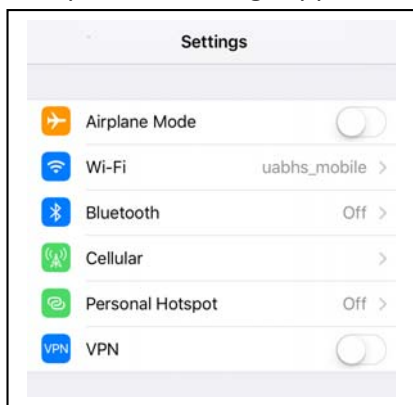
- Identify eligible patients through medical record review, clinical referral
- Research coordinator will call potential participants based on inclusion criteria.
- If participant agrees to participate complete screening form and depending on urate level and last lab values, may need to get new lab values before enrollment.
- If lab values need to be collected before study inclusion, ask patient to arrive 1 hour early to have new labs recorded
- Once lab values are available determine eligibility
 - IF NOT eligible, thank participant for their time and place screening form in binder
 - If participant is eligible, they will need to complete an enrollment form, consent form and W9 for the study
 1. Confirm smart phone is up to date on operating system (iOS 8 and up and android 4 (Jellybean and up)
 2. Confirm phone enough memory to download Fitbit app
 - iPhone
 - To check available memory open the settings app and under the general tab there is a tab labeled storage and iCloud usage.
 - The available storage will be listed, and if changes need to be made they can be addressed under “manage storage”



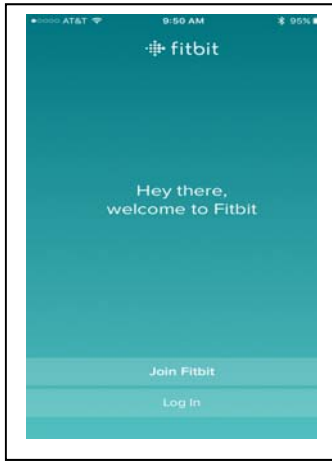
- Android
 - To check available memory open the settings app and open the storage tab to find the available storage
 - If changes need to be made apps or text messages can be deleted



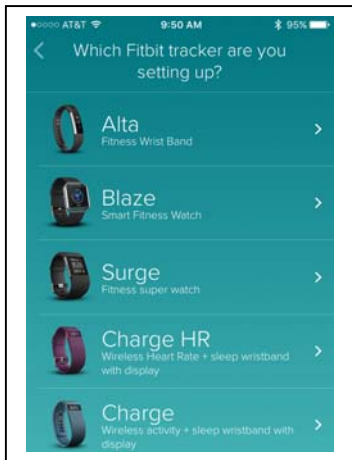
- Place screening form, enrollment form, consent form, and W9 in study binder
- Please be sure that the participant has entered a valid phone number and an email address
 1. Place test call to phone number provided to make sure it is valid
 2. Review email address to ensure it is valid (eg. no555@555.com), and it is legible
- Pull randomization assignment from study binder and add study ID to screening and enrollment form
- Begin Fitbit for smart phone installation (Be sure to write Fitbit serial number (located on bottom of box) in the enrollment log page in study binder
 - Turn on Bluetooth and ensure location is turned on
 1. Open the settings app and turn on Bluetooth



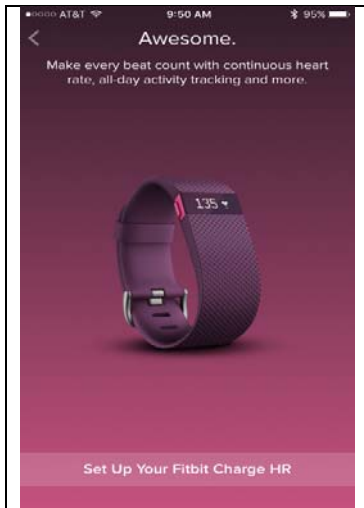
- Download Fitbit app from apple store or Google play store
 1. If memory full, ask participant what can be deleted to accommodate the app
 2. If participant doesn't want to delete, they are not eligible for the study
- You will be prompted to create an account. Please press "Join Fitbit"



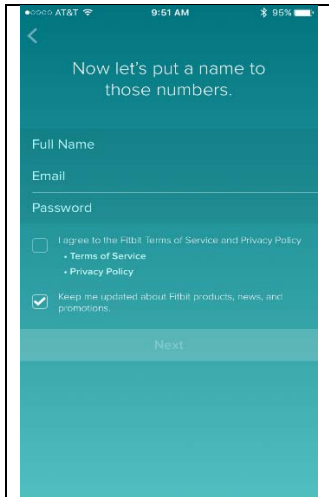
- Select the Charge HR model



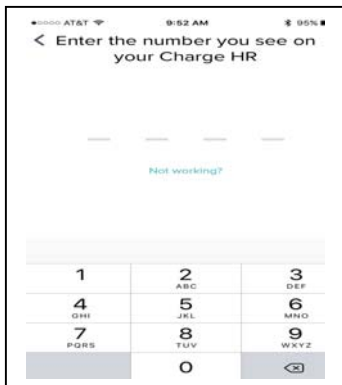
- Continue through the prompts "Set Up Your Fitbit Charge HR"



- Enter participant height, gender, weight, and birthdate
- The next screen will require the participants full name, email and password.
 1. They will need to agree to the terms of use, and uncheck the option to receive updates about Fitbit products, news, and promotions.
 2. Confirm email address matches email on consent form. If not please make a note



- On the next screen they will need to agree once again to the terms of service by tapping “next”
- Next a 4-digit number will be displayed on the Fitbit and the number will need to be entered into the app. **Make sure other Fitbits are out of range to avoid a sync issue.**



- The participant is now ready to use the Fitbit
- **Don't forget to document Fitbit serial number (located on bottom of box) in the screening log**
- Double check the app has been installed and double check the phone and Fitbit are able to sync properly
- Review how to charge Fitbit, (proper use of the Fitbit charging cable)

10.2.1.1 RheumPRO Arm

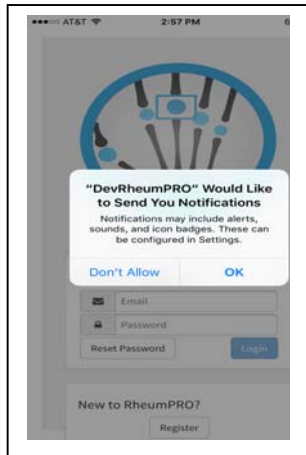
- RheumPRO app installation
 - Coordinator will type in web address to access RheumPRO application
 1. Web Address <https://dev-rheumpro.hs.uab.edu/goutpro/>
 - Once participant accesses the link via their smart phone, identify the operating system, either iPhone or Android
 - There is a possibility of connectivity issues with the RheumPRO app
 1. for Android Users it will prompt the download of the APK which they can then install.
 2. There have been documented issues opening the app and using the features while on the UAB Wi-Fi.
 3. If you are unable to connect try another Wi-Fi network
 4. If unsuccessful try downloading the app or reloading app page using cellular data

- After password is entered, a page description of the app, click on “install application will be seen, and a pop-up window will appear to confirm installation



- Once the install application button has been selected, there are a series of direction on the screen prompting the participant to be sure the installation has proceeded. Helpful pointers are listed below:
 1. “in progress”:
 - Installation will be performed in the background (since iOS7): check the icons on device’s home screen
 2. “or not”
 - If the iOS popup “Would you like to install...” did not appear, check that participant doesn’t already have the same app installed from the AppStore
 - If an app with the same bundle identifier is already installed on the device from the AppStore, nothing will happen
 - Delete the app installed from the AppStore to be able to install this one
 3. “Nothing seems to happen”
 - After tapping the “install” button in the popup, if nothing seems to happen and participant is still on the same page, check device home screen: the installation should be in progress: should see the icon of the app somewhere and a progress bar
 4. “Unable to download app popup”
 - First check internet connection, and be sure that device is not behind a firewall that may prevent downloading .ipa files
 - Most common installation issues are:
 - Expired provisioning profile
 - Incompatible device (check iOS version, device family, and required device capabilities)
 5. If a popup with “untrusted enterprise developer” is displayed.

- Direct participant to settings -> General-> Device Management-> Click on appropriate Enterprise App (University of Alabama at Birmingham and click trust
 - Add layout for android
6. Now go back to homepage and click on app
 7. Popup window will be displayed when app is opened requesting “DevRheumPRO would like to send you notifications, press “OK”



8. If new to RheumPRO click on register
9. The app will prompt you to reference the physical consent document for the study. It will ask you to press next
10. The next screen will ask the participant to answer whether they have signed the physical consent document
11. If they have, press agree and a new screen will ask them to sign with their finger and type in their name and submit

12. The next several screens require the participant to create an account. They will need to provide (the questions are spread out over 4 separate screens):

- Email address
- Password
- First/Last Name
- Relationship to Arthritis: Patient, Caregiver, etc.
- Sex
- Race
- Date of Birth
- Country
- Zip Code

Step 2 of 4

First Name:

Last Name:

Relationship to Arthritis:

Sex:
 Male
 Female

Race:

Hispanic:

Date of Birth:

Twitter Handle: Optional

- Twitter Handle is not a required field**

Step 3 of 4

Country:
 United States of America

Postal Code:
 00000

A valid zipcode is required

Filling in the optional fields below may help us personalize your news, research opportunities and link your account to other services more efficiently in the future.

State: Optional
 Select State

City: Optional
 City

Address Line 1: Optional
 Street/PO Box/etc

Address Line 2: Optional
 Apt/Suite/etc

Previous Next

- Postal Code/Zip is required; address is not **

Step 4 of 4

Select diseases that you have been diagnosed with:

Ankylosing Spondylitis
 Dermatomyositis
 Fibromyalgia
 Gout
 Inflammatory Bowel Disease
 Juvenile Idiopathic Arthritis
 Lupus
 Osteoarthritis (degenerative arthritis)
 Osteoporosis/Osteopenia/low bone mineral density
 Polymyositis
 Psoriasis
 Psoriatic Arthritis
 Rheumatoid Arthritis
 Scleroderma (systemic sclerosis)

Select Insurance

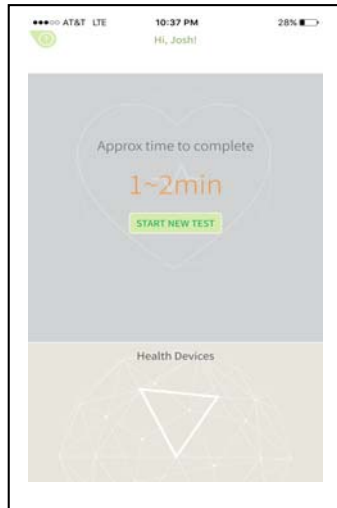
Medicare
 Medicare Advantage
 Medicaid
 Tri-care / Military
 Commercial/Private insurance
 Other type of insurance
 No insurance

I Have a Rheumatologist

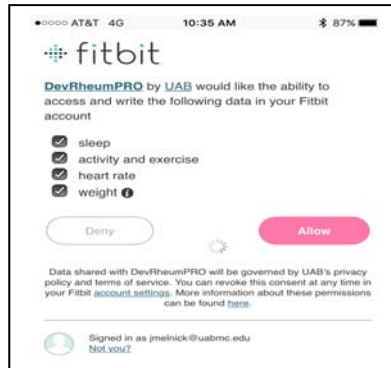
Previous Submit

- There is no need to click on the “I have a rheumatologist” button. It is not necessary for the app registration**

13. Upon completion of registration the app homepage will be displayed. In order to give permission for RheumPRO to access the Fitbit data, click on “Health Devices”



14. An icon with “Fitbit” and a “+” will be displayed.
15. Click on the “+” to add the participants Fitbit.
16. A log-in page will be displayed and the participant will need to add their Fitbit login credentials
17. A new page will be displayed asking for permission to access the Fitbit data. We want to have access to all 4 fields. Press Allow to complete authorization



18. The next page will be a confirmation screen, and hit done in the bottom left corner to return to the home page.
19. The initial flare assessment should be available to complete. Please make sure the participant completes this survey before leaving

- Provide participant with reminder and trouble-shooting pamphlet.
 - Don’t forget to fill in study ID, RheumPRO account information, and Fitbit account information.

10.2.1.2 IVR Study Arm

- After download of Fitbit app, patient will need to log-on to website to register with IVR system
- Website to log-in: **secure.aging.uab.edu**
 - Password: **saag6086gout**



Division of Gerontology, Geriatrics, and Palliative Care Logon Page

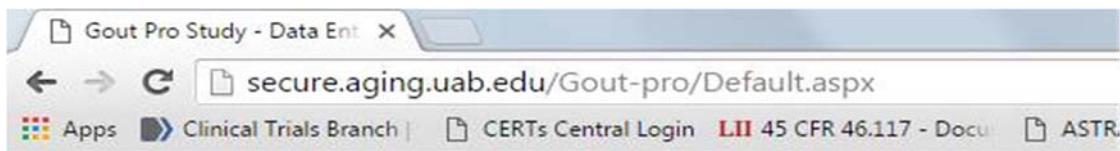
This page is used to access documents.


Palliative Care Resident Library

Study of Aging

Gout Pro Study

- Once password has been entered on website, please have the following information ready
 - Study ID
 - Patient preferred phone number
 - Preferred Call Time



This page is for data entry. 

Subject ID:
Subject phone number:
Preferred call time (Format military time HH:MM):

- Immediately after entering information into webpage a call will need to be placed to IVR system
 - **(205-996-3851) enter 222 and then the study ID**
- Enter study ID using keypad into IVR
- Record patients name, using their own voice and complete first flare assessment using touch-tone keypad on smart phone: **IVR Phone Number: 205-996-3851**
- Make sure the coordinator writes down the preferred call time for IVR system and preferred phone number for future calls
- Remind participant of IVR call schedule.
 - Will be conducted weekly throughout the study period
 - Participant will designate a time for phone calls to be made
 - Confirm preferred phone number for IVR calls

- Provide participant with reminder card and trouble-shooting pamphlet
 - Card will have study ID and phone number
 - Remind participant that study ID will be entered into IVR to confirm participation
- At the end of the visit, the coordinator will send enrollment form, consent form, W9, and preferred phone number, and call time to UAB (fax #: 205-975-6859)

10.2.2 Visits 2-12

- Visits 2-12 will be completed by participant using IVR or RheumPRO application
- Participants will receive notification the day of, 24 hours, and 48 hours later
 - IVR will call participant at designated time to complete
 - RheumPRO will send push notifications participants to complete survey

10.2.3 Visit 13 (Crossover Visit)

- Coordinator will call/schedule crossover visit 7 days in advance and remind participant to bring smart phone and Fitbit
- Patients will return to clinic to complete crossover visit to switch to the opposite arm of the study

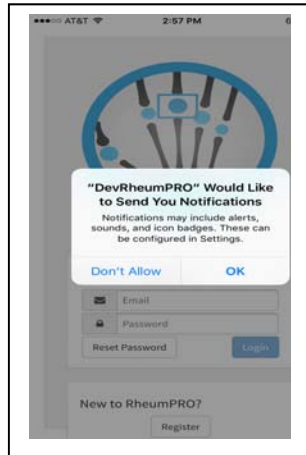
10.2.3.1 *New RheumPRO participant*

- RheumPRO app installation
 - Coordinator will type in web address to access RheumPRO application
 1. Web Address <https://dev-rheumpro.hs.uab.edu/goutpro/>
 - Once participant accesses the link via their smart phone, identify either iPhone or Android
 - There is a possibility of connectivity issues with the RheumPRO app
 1. For Android Users it will prompt the download of the APK which they can then install.
 2. If you are unable to connect try another Wi-Fi network
 3. If unsuccessful try downloading the app or reloading app page using cellular data
 - After password is entered, a page description of the app, click on “install application will be seen, and a pop-up window will appear to confirm installation



- Once the install application button has been selected, there are a series of direction on the screen prompting the participant to be sure the installation has proceeded. Helpful pointers are listed below:
 1. “in progress”:
 - Installation will be performed in the background (since iOS7): check the icons on device’s home screen
 2. “or not”
 - If the iOS popup “Would you like to install...” did not appear, check that participant doesn’t already have the same app installed from the AppStore
 - If an app with the same bundle identifier is already installed on the device from the AppStore, nothing will happen
 - Delete the app installed from the AppStore to be able to install this one
 3. “Nothing seems to happen”
 - After tapping the “install” button in the popup, if nothing seems to happen and participant is still on the same page, check device home screen: the installation should be in progress: should see the icon of the app somewhere and a progress bar
 4. “Unable to download app popup”
 - First check internet connection, and be sure that device is not behind a firewall that may prevent downloading .ipa files
 - Most common installation issues are:
 - Expired provisioning profile
 - Incompatible device (check iOS version, device family, and required device capabilities)
 5. If a popup with “untrusted enterprise developer” is displayed.
 - Direct participant to settings -> General-> Device Management-> Click on appropriate Enterprise App (University of Alabama at Birmingham and click trust
 - Add layout for android
 6. Now go back to homepage and click on app

- Popup window will be displayed when app is opened requesting “DevRheumPRO would like to send you notifications, press “OK”



7. If new to RheumPRO click on register
8. The app will prompt you to reference the physical consent document for the study. It will ask you to press next
9. The next screen will ask the participant to answer whether they have signed the physical consent document
10. If they have, press agree and a new screen will ask them to sign with their finger and type in their name and submit
11. The next several screens require the participant to create an account. They will need to provide (the questions are spread out over 4 separate screens):
 - Email address
 - Password
 - First/Last Name
 - Relationship to Arthritis
 - Sex
 - Race
 - Date of Birth
 - Country
 - Zip Code

Step 2 of 4

First Name:
First Name

Last Name:
Last Name

Relationship to Arthritis:
Select Relationship to Arthritis

Sex:
 Male
 Female

Race:
Select Race

Hispanic:
Select Hispanic

Date of Birth:
[Dropdown]

Twitter Handle: **Optional**
Twitter Username

Previous Next

- Twitter Handle is not a required field**

Step 3 of 4

Country:
United States of America

Postal Code:
00000

A valid zipcode is required

Filling in the optional fields below may help us personalize your news, research opportunities and link your account to other services more efficiently in the future.

State: **Optional**
Select State

City: **Optional**
City

Address Line 1: **Optional**
Street/PO Box/etc

Address Line 2: **Optional**
Apt/Suite/etc

Previous Next

- Postal Code/Zip is required; address is not **

Step 4 of 4

Select diseases that you have been diagnosed with:

Ankylosing Spondylitis

Dermatomyositis

Fibromyalgia

Gout

Inflammatory Bowel Disease

Juvenile Idiopathic Arthritis

Lupus

Osteoarthritis (degenerative arthritis)

Osteoporosis/Osteopenia/low bone mineral density

Polymyositis

Psoriasis

Psoriatic Arthritis

Rheumatoid Arthritis

Scleroderma (systemic sclerosis)

Select Insurance

Medicare

Medicare Advantage

Medicaid

Tri-care / Military

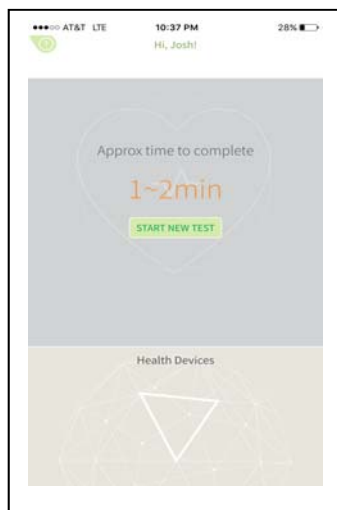
Commercial/Private insurance

Other type of insurance

No insurance

- There is no need to click on the “I have a rheumatologist” button. It is not necessary for the app registration**

12. Upon completion of registration the app homepage will be displayed. In order to give permission for RheumPRO to access the Fitbit data, click on “Health Devices”



13. An icon with “Fitbit” and a “+” will be displayed.
14. Click on the “+” to add the participants Fitbit.
15. A log-in page will be displayed and the participant will need to add their Fitbit login credentials
16. **A new page will be displayed asking for permission to access the Fitbit data. We want to have access to all 4 fields. Press Allow to complete authorization**



17. The next page will be a confirmation screen, and hit done in the bottom left corner to return to the home page.

18. The initial flare assessment should be available to complete. Please make sure the participant completes this survey before leaving

- Provide participant with reminder card and trouble-shooting pamphlet
 - Don't forget to fill in study ID, RheumPRO account information, and Fitbit account information.

10.2.3.2 New IVR Participant

Before crossing over participants to the IVR, the participant will need to have the RheumPRO app uninstalled from their smart phone. To uninstall app: hold down on the desired app to uninstall. Once the app begins to shake, tap the x in the top left corner to delete the app from the phone

- First uninstall the RheumPRO app by holding down on the app until it starts to wiggle. Tap the "X" in the top left corner and confirm deletion.



- After uninstalling of RheumPRO app, patient will need to log-on to website to register with IVR system
- Website to log-in: secure.aging.uab.edu
 - Password: **saag6086gout**



Division of Gerontology, Geriatrics, and Palliative Care Logon Page

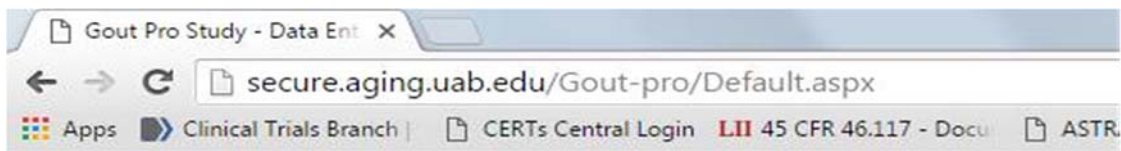
This page is used to access documents.


Palliative Care Resident Library

Study of Aging

Gout Pro Study

- Once password has been entered on website, please have the following information ready
 - Study ID
 - Patient preferred phone number
 - Preferred Call Time



This page is for data entry. 

Subject ID:
Subject phone number:
Preferred call time (Format military time HH:MM):

- Immediately after entering information into webpage a call will need to be placed to IVR system
 - **(205-996-3851)**
- Enter study ID using keypad into IVR
- Record patients name, using their own voice and complete first flare assessment using touch-tone keypad on smart phone
- Make sure the coordinator writes down the preferred call time for IVR system and preferred phone number for future calls
- Remind participant of IVR call schedule.
 - Will be conducted weekly throughout the study period
 - Participant will designate a time for phone calls to be made
 - Confirm preferred phone number for IVR calls

- Provide participant with reminder card and trouble-shooting pamphlet
 - Card will have study ID and phone number
 - Remind participant that study ID will be entered into IVR to confirm participation
- At the end of the visit, the coordinator will need to send enrollment form, consent form, W9, and preferred phone number, and call time to UAB
 - Send all forms the same day to 205-975-6859

10.2.4 Visits 14-26

- Phone IVR/RheumPRO Visit by patient
- Participants will receive notification the day of, 24 hours, and 48 hours later
 - IVR will call at designated intervals to complete
 - RheumPRO will send push notification to complete survey

10.2.5 Unscheduled Visit (IVR/RheumPRO report initiated by patient)

In the event a participant experiences multiple flares in a single week participants have the ability to enter flare information on an ad hoc basis.

- IVR: 205-996-3851
 - Call into the system, enter study ID and begin assessment
- RheumPRO
 - Log into RheumPRO (open app) tap to complete flare assessment to being survey

10.2.5.1 RheumPRO Participant

- In the event that the participant has a gout flare in-between the scheduled weekly surveys the participant can open the RheumPRO app and complete a survey
 - Describe the process of opening the app and finding the interval gout flare assessment survey icon to the participant
 - Stress to them the importance of completing this form ONLY when they feel they are having a gout flare

10.2.5.2 IVR Participant

- In the event the participant has a gout flare in-between the scheduled weekly surveys, the participant can make an unscheduled call to the IVR system to report their flare
 - Review the process for completing the flare assessment via the IVR
 - The phone number and study ID can be found on the reminder card
 - The IVR phone number to call is **205-996-3851**
 - The will need to enter their study ID using the touch tone key pad and then they will be able to complete the flare assessment

11 Data Collection, Study Forms, and Logs

All data for this study will be collected by study staff in accordance with 21 CFR Part 11 rules and will meet all regulatory requirements.

11.1 Study Participant Forms

Data will be collected by the study staff at each visit on study forms as described and presented below:

Form	Description	Visit administered	Instructions	Location
Informed consent	Informed consent	Visit 1	Participant reads through consent and initials each page in the box. Participant, doctor obtaining consent and study staff should all sign, date and time stamp	Tab 2.2 Study Binder
Paper Screening (Patient)	Ensures eligibility by determining that all inclusion criteria are met.	Pre-visit Phone call	Completed by study staff via phone call preceding initial exam. Certified by study coordinator.	Tab 2.3 Study Binder
Paper Screening (Physician/Staff)	Quick sheet to ensure eligibility by determining that all inclusion criteria are met	Visit 1	Completed by study staff prior to initial exam	Tab 2.4 Study Binder
Paper Enrollment	Detailed contact sheet for participant and one other listed contact	Visit 1	Participant is asked for contact information for his/herself and one other person	Tab 2.5 Study Binder
W9 Form for Patient Honoraria	W9	Visit 1	Completed by patient to receive study payment	Tab 2.6 Study Binder
FAQ Sheets	FAQ Sheets for IVR and RheumPRO	Visit 1 and 13	Participant FAQ sheets to help with any unanswered questions	Tab 2.7 Study Binder

11.2 Study Specific Administrative Forms, Logs, and Data Tables

Form	Description	Location
Schedule of Visits and Evaluations	Listing of all schedule study visits and evaluations	Tab 4.1 Study Binder
Training log	Record of trained study personnel	Tab 4.2 Study Binder

Screening log	Log of individuals screened and enrolled	Tab 4.3 Study Binder
Telephone Contact Log	Record of all calls between study staff and participants. Study coordinator(s) complete log showing interval visit calls.	Tab 4.4 Study Binder
Protocol deviation log	A record of all of the protocol deviations that occur throughout the study. It contains explicit instructions for recording the incident and should be updated each time a deviation occurs.	Tab 4.5 Study Binder
Study Completion form	Record of participant study completion/withdrawal	Tab 4.6 Study Binder
Paper Screening (Patient) Phone Script	Phone Script for Paper Screening call to determine eligibility and potential update of labs prior to clinic visit	Tab 4.7 Study Binder

12 Data Management

Data management will be the responsibility of the research assistants, study coordinator, project manager and study statistician. The study statistician will oversee the data management, training coordinators to ensure proper data entry, editing and updating will be the responsibility of the research assistants, while tracking and corrections will be the responsibility of the entire staff. All data will be exported into SAS files and stored on a secure and encrypted server or hard drive. From these data sets, logic among the variables and out of range checks will be conducted every 2 weeks. The study statistician will develop validity checks for outlier values, consistency, and completeness and will notify the principal investigator if issues are identified. Discrepancies will be adjudicated by consultation with the principal investigators. Once data entry is complete, the study data will be transferred to SAS statistical software and reviewed by the statistician. All efforts will be made to ensure the data is in compliance with the UAB Institutional Review Board (IRB) policies, Good Clinical Practice (GCP) guidelines, and Federal regulations.

12.1 Data Entry

Data collected by RheumPRO and IVR will be downloaded from IVR and RheumPRO databases and entered into an excel spreadsheet. Data from screening and enrollment paper forms will be entered directly into the excel spreadsheet by the UAB Study Coordinator. Data entered into the system will be downloaded every two weeks and the database will have range and validity checks built in.

12.1.1 General Instructions for Completing Paper Forms

All data will be maintained according to FDA and ICH Good Clinical Practice (GCP) guidelines. Instructions for completing Case Report Forms (CRFs) to ensure quality and consistency in data collection are below.

12.1.2 Sample instructions

When completing paper study forms participants must not be identified by name on any study document submitted with the forms. Replace the participant name with the participant initials and identification (ID) number.

12.1.3 Header

Complete the header information in every field, including fields for which no study data are recorded. From the drop down box choose Not Applicable, Unknown, or UNK for fields where no data can be provided.

12.1.4 Study ID

The Study ID will be prepopulated in the header of the screening and enrollment pages

12.1.5 Dates

All dates will be verified by the study coordinator. Historical dates are sometimes not known (e.g., date of first symptom); in this case, chose Not Applicable, UNKNOWN or UNK to indicate missing data.

12.1.6 Completion of forms

All paper forms must be completed and saved in the database. The study team member responsible for the entry of data into the database must ensure that all fields have been completed and that the form has been saved and marked as complete. If a form cannot be completed or data cannot be verified the form should be marked incomplete or unverified. Forms should only be marked unverified if PI or investigator review is required.

12.1.7 Missing or Incomplete data

Data may not be available to complete the forms for various reasons. Forms with missing data in fields or sections should be marked as INCOMPLETE in the study database. Indicate the reason for the missing data in the text field when available.

12.1.8 Incomplete or Illegible forms

If any section or an entire page of the forms cannot be completed (e.g., no parts have any responses), and it is unlikely that it will be completed, indicate NOT DONE/ND, NOT AVAILABLE/NA or NOT APPLICABLE/NAP, as appropriate. Do not leave forms incomplete or unused without explanation.

All form header information must be completed even though no data are recorded on the electronic form. If an electronic form can only be partially completed at the time of visit, but will be completed when the information becomes available, note this in the MISSING FORMS / INCOMPLETE FORMS field and follow the direction of the study coordinator and principal investigator.

13 Analysis Plan

Since the study is a pilot study to demonstrate feasibility of recruiting and training gout patients to utilize RheumPRO and IVR, a priori sample size calculations were not performed. We will summarize baseline characteristics of study participants as means with standard deviation (SD) for continuous and ordinal measures and number and percentage for categorical variables. All statistical analyses followed standard methods for a 2-by-2 crossover design. Preference and satisfaction surveys will use dichotomous questions and/or a Likert scale (range 0 to 10; very easy to very difficult). Differences between the RheumPRO and IVR approach will be evaluated using McNemar's test for dichotomous variables, paired t test for continuous variables, and nonparametric Wilcoxon signed rank test for ordinal variables. Qualitative questionnaire data for lack of response will be summarized as percentages. We will conduct sensitivity analyses with multiple imputations to examine the robustness of the reported results and the effects of missing data for both the as-treated and intent-to-treat populations. A two-sided alpha of 0.05 will be used to determine significance.

For comparisons of Fitbit® wear compliance data, descriptive statistics with proportions will be used. To study the changes in sleep and step counts on days when the participant reported a gout flare, we will use a mixed linear model to account for repeated observations and to adjust for potential confounders. The pattern of wear time for each participant over the course of the 6 month study will be examined descriptively using a heat map and colored as compliant wear with sleep days (red), compliant wear without sleep days (green), partial wear (blue) days, and no health tracker data (White) days. We will measure the association of flare with mean step counts and sleep duration collected from the wearable tracker device, comparing flare days to non-flare days. An alpha of 0.05 will be used to determine significance. All analyses will be performed with SAS (version 9.4, SAS, Cary, NC).

14 Study compliance

Protocol deviations will be tracked using the log below and notification of appropriate parties (UAB IRB) should take place following a deviation in the period specified by each party.

Protocol deviations include, but are not limited to, the following:

- Randomization of an ineligible participant
- Failure to obtain Informed Consent
- Entering a participant into another study
- Failure to keep IRB approval up to date
- Wrong treatment administered to participant

All deviations will be reported to the appropriate parties, including the Principal Investigator and to the IRB as soon as they are discovered. The study staff and research assistants will maintain the log of all protocol deviations

15 Quality Control and Standard Operating Procedures

All study procedures are to take place at UAB and UNMC and will do so in accordance with the Protocol.

15.1 Data and Form Control

Study files will be monitored by research assistants on a weekly basis, and will also be monitored by other study staff members (study coordinator, manager, statistician, and PIs) on a monthly basis to ensure quality control. The appropriate regulatory and IRB documentations will be kept on file and up to date by the research assistants and administrative staff.

15.1.1 IRB documents

- All IRB Correspondence is on file
- The study staff are IRB approved prior to performing any study procedures
- Adverse events and deviations are reported to IRB per current guidelines
- All versions of the IRB protocols and informed consent forms are on file
- Reporting all protocol deviations (exceptions and violations) are reported to IRB as required and documented in the participant chart.

15.1.2 Informed Consent

- Ensure that participant identification is on all pages of the ICF
- There is documentation that the participant is given a copy of the consent form
- The participant and study representative signed and dated the consent form for him/herself.
- The participant initialed and dated all appropriate pages on the informed consent form.
- Note to file made for any informed consent deviations.
- Ensure a valid (current version date) copy of the consent form was used
- Contact information collected on study participant and two additional study contacts.

15.1.3 Protocol

- Confirm that the study staff is conducting the study in compliance with the protocol approved by IRB.
- The protocol deviations (exceptions and violations) are documented appropriately and reported to IRB as required.

15.1.4 Case Report Forms

- Review participant files to ensure that accuracy, and completeness of the data
- Any correction made to the CRFs will be updated in the spreadsheet. The original entry is archived and hard copies can be printed.
- Note files made for missing or incomplete data and to explain any discrepancies or additional comments in appropriate text fields.

15.1.5 Other documents

- CVs for all study staff are on file and updated every 2 years
- Medical licenses for the PIs and Co-Investigators are on file and updated prior to expiration

- Delegation Log is updated as new staff are added or removed from the study or new procedures are added
- Yearly financial disclosures for PIs and consultants

15.2 Clinical Monitoring

Sites will be monitored by the PIs at each respective site (UAB or UNMC) according to established monitoring standard operating procedures (SOPs).

15.3 Reports

Reports as outlined in the communications plan above will be prepared to keep the study staff up to date and engaged, as well as help to check quality control. These reports will take the form of:

- Weekly status emails to the PI by the research assistants and study coordinator
- Monthly reports that will be compiled by the research assistant and staff statistician in presentation form for study meetings will include
 - Target and actual enrollment,
 - Individuals screened with reasons for screen failure,
 - Enrollment status (enrolled, active, completed, discontinued treatment, and lost to follow-up).
 - Electronic forms completed and entered
 - Missing or erroneous data.

16 Study Closeout

At the conclusion of the study the following procedures will be done to verify all study related obligations have been met. Verification that all study procedures have been completed including, but not limited to the following procedures includes:

- All data has been collected
- All data queries have been completed.
- All electronic source materials have been properly documented and archived
- Any study related supplies and unused medication is returned for destruction.
- Assurance that correspondence and study files are accessible for audits.
- Reminder to investigators of their ongoing responsibility to maintain study records and to report any relevant study information to the study safety officer
- IRB notification of the study completion and stored copy of the notification.
- Preparation of a report summarizing the study's conduct and results.
- Participant notification of the study completion.

17 Participant Notification

Upon enrollment participants will be asked if they would like to be notified and/or receive copies of study reports and publications. Those participants who are interested in receiving these materials will be mailed/emailed copies to the address they provide.

18 Policies

All staff will be instructed in their study specific responsibilities regarding data safety and confidentiality. Additionally all staff will be cautioned against the release of data to any unauthorized individuals and no data will be released to any individual without first obtaining approval from Amgen and/or the UAB IRB.

This section of the Protocol will discuss the safeguards which have been put in place by the PIs to ensure participant confidentiality and data security.

The following is a list of study participant confidentiality safeguards:

- Data flow procedures – As this is a two site study and therefore data identifying participants will be transmitted between sites. The study statistician and coordinator will provide thorough data entry and confidentiality training to all staff involved in data collection and data entry. All CRFs and copies will be included in participant electronic study binder on day of visit or phone check in. The study statistician, project manager, and coordinator will review all data collected weekly to ensure all forms are being completed correctly into the study database and are intact. Data from UNMC will be faxed to UAB weekly.
- Electronic files – All data identifying participants will be stored electronically will be maintained by the study statistician and will be encrypted at all times.
- Data listings – Data or information containing the participant name, study ID, medical information, record number, Social Security Number, or any other unique identifier will under no circumstances be included in any published data listing.
- Data distribution - data listings that contain participant name, name code, or other identifiers easily associated with a specific participant will not be distributed.
- Data disposal - computer listings that contain participant-identifying information should be disposed of in an appropriate manner.
- Access - participant records stored in the data center should not be accessible to persons outside the center without the express written consent of the participant.
- Storage – All data collected during this will be stored on UAB Department of Medicine Servers and UNMC Servers. Any printed study forms and related documents created both during and after study completion will be stored in a secure location in UAB Faculty Office Tower. Printed study forms and related documents from UNMC will be faxed securely to UAB weekly.
- Passwords – Each study related file will be password protected. Additionally, limitations will be placed on general access to the study's database and to the functions that individuals can use. All passwords will be changed on a regular basis.
- User Training - Study staff with access to clinical computer systems will be trained in their use with an emphasis on, and the importance of, system security.
- System Backups - Backup copies of electronic data will be made weekly by the study coordinator or study statistician. Hard copy backups will be printed and stored in locked file cabinets in secure areas with limited access at the end of the study.

19 Publications

It is mandatory that the first publication will be based on data from both centers that has been analyzed as stipulated in the protocol. Participating PIs agree not to present data gathered from one center before the full publication, unless formally agreed to by all other PIs.

20 Protocol Maintenance

The Protocol will be maintained and updated throughout the study by the study staff as necessary. The most current copies of the Protocol will be kept on a shared project drive, and a hard copy, in loose leaf form, will be kept in staff issued binders along with other study files for staff for their reference. Each page of the Protocol is numbered, dated, and contains the version number to eliminate any confusion. As a living document the Protocol will be continuously reviewed by study staff to ensure the operating procedures described are accurate. If any procedures are changed or modified, the Protocol will be updated and the new version will be emailed and printed for study binders for all study staff members.

21 References

1. Garg R, Sayles H, Yu F, Michaud K, Singh J, Saag K, et al. Gout-related health care utilization in US emergency departments, 2006 through 2008. *Arthrit Care Res.* 2013;65(4):571-7.
2. Becker MA, Schumacher HR, Wortmann RL, MacDonald PA, Palo WA, Eustace D, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: A twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum.* 2005;52(3):916-23.
3. Becker M, Schumacher H, Wortmann R, MacDonald P, Eustace D, Palo W, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005;353(23):2450-61.
4. Schumacher H, Becker M, Wortmann R, Macdonald P, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* 2008;59(11):1540-8.
5. Becker M, Schumacher H, Espinoza L, Wells A, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. *Arthritis Res Ther.* 2010;12(2).
6. Sundy J, Baraf H, Yood R, Edwards N, Gutierrez-Urena S, Treadwell E, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: Two randomized controlled trials. *JAMA.* 2011;306(7):711-20.
7. Borstad G, Bryant L, Abel M, Scroggie D, Harris M, Alloway J. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J Rheumatol.* 2004;31(12):2429-32.
8. Taylor WJ, Schumacher HR, Baraf HSB, Chapman P, Stamp L, Doherty M, et al. A modified delphi exercise to determine the extent of consensus with OMERACT outcome domains for studies of acute and chronic gout. *Ann Rheum Dis.* 2008;67(6):888-91.
9. Taylor WJ, Shewchuk R, Saag KG, Schumacher HR, Singh JA, Grainger R, et al. Toward a valid definition of gout flare: Results of consensus exercises using delphi methodology and cognitive mapping. *Arthritis Rheum.* 2009;61(4):535-43.
10. Gaffo AL, Schumacher RH, Saag KG, Taylor WJ, Dinnella J, Outman R, et al. Developing a provisional definition of flare in patients with established gout. *Arthritis Rheum.* 2012;64(5):1508-17.