Title: The Influence of a Medication Adherence Smartphone Application on Medication Adherence in Chronic Illness
NCT #: 05098743
Date of Protocol and Statistical Analysis Plan: 12/03/2021

Study Protocol:

A) RECRUITMENT *:* The principal investigator (PI) will use the following recruitment strategies: in-person recruitment and clinician referral through use of the study flyer/referral form.

In-person recruitment: The PI will be present at the health center(s) on multiple days/week when health care providers (HCPs) and clinic staff see patients. The PI will work closely with HCPs and clinic staff to identify eligible patients and to how/when best approach eligible patients to introduce them to the study, anticipating it might be at the end of the visit in the exam room. The HCPs and clinic staff will introduce the PI to potentially eligible patients to introduce the study prior to the PI approaching the patient. Once the patient expresses interest in learning more about the study or indicates they would like to participate, the PI will follow the procedures as outlined in the study procedure section below. Eligibility: 1) adults aged 18 years and older 2) speak and understand English 3) personally own and use an Android or iOS smartphone which is capable of downloading the Medisafe app and
4) take at least 1 medication for a chronic illness based on their computerized medical record at the health center.

Clinician referral: Study flyer/referral forms will be available in the patient exam rooms and/or in the medicine department's clinician office as determined/approved by clinic staff. Once a clinician identifies a potentially eligible patient, they or the patient may complete the study flyer/referral form. If the PI is present at the clinic, the form can be given directly to the PI. If the PI is not available, they will place it in a locked and secured collection box labeled "Smartphone App Study" only accessible by the PI. The box will be located in the general medicine department's clinician office or the appropriate exam rooms or as otherwise deemed necessary by clinic staff. The box will be checked, and forms collected at least once a week by the PI. Any patients who fill out a form will be contacted via their preferred method i.e., phone call, email or text message (see scripts for a phone call, email or text message) within one week by the PI.

Study flyer/referral form: Study flyers/referral forms will provide study information and a place for patients interested in participation to provide their contact information as well as a space for the referring HCP signature to confirm that the patient's medications listed in the Electronic Medical Record are correct and up-to-date. The flyers will be kept in exam rooms deemed appropriate by clinic staff and will be returned to the HCP. The HCP will then either give them to the PI or place them in a secured collection box labeled "Smartphone App Study" which will only be accessible to the PI. The box will be checked at least once a week, and forms will be collected at that time by the PI.

B) STUDY PROCEDURES:

Once patients are contacted, the completed flyer/referral forms will be placed in a locked file cabinet at the clinic accessible to only the PI. The patient's name, contact information and preferred mode of contact will be housed in REDCap, a HIPAA compliant, password protected database application.

For patients who are available in-person: If a patient expresses interest in participating, the PI will meet with the patient in a private room at the clinic to confirm eligibility, describe the study, answer questions and, based on patient preference, obtain e-consent using an iPad or a hard copy of the consent form. Once the patient is consented, the PI will obtain a printed-out copy of the patient's updated, current medication list from the EMR. The medication list will be reviewed by the PI to confirm that the patient regularly takes at least 1 prescribed medication for a chronic illness. Based on patient preference, the PI will then either give them a hard copy of the survey, or direct them to the REDCap survey on the PI's iPad. While patients complete the survey, the PI will remain in the room to be available should questions arise, but will be distanced away from the patient.

For patients whose completed flyer/referral form is collected from the lock box:
Once the PI contacts patients and they indicated an interest to participate, the PI will obtain their permission to email them the link to the IRB approved econsent form, which will be followed by the REDCap survey, if they prefer this method. If they prefer scheduling a time to complete this at the clinic, a time will be arranged.

Informed consent: For eligible patients interested in participation, the PI will obtain either in-person written consent or in-person IRB-approved e-consent via REDCap on an iPad. If the patient is not present in the clinic and would like to receive the IRB approved e-consent form via email, the patient will be sent an email link to the REDCap e-consent survey to access study information. Hard copies of consent forms will be kept in the locked file cabinet.

C) DATA COLLECTION METHODS:

1.) Survey

a)*Baseline Data Collection (Time 1): Survey (both intervention and waitlist control groups)*: Once consent is obtained, the PI will administer the baseline questionnaire as either a hard copy survey or the REDCap electronic survey on a password protected iPad if the patient prefers. The patient will complete the baseline questionnaire independently, unless they ask for the PI to assist, in which case the PI will read each question to the patient with the patient indicating their answer on either the iPad or the hard copy survey. Only if the patient requests that the PI indicate their responses on the survey will the PI fill out the questionnaire for the patient. The PI will be present to answer any questions patients may have during data collection.

Hard copy surveys: The completed hard copy surveys will be kept in a locked file cabinet at the health center. All hard copy surveys will be assigned the unique study identifier (REDCap ID) and any patient identifiers will be removed / blacked out prior to storage. The PI will enter data collected using hard copy surveys once into the main REDCap database and into a second REDCap database to enhance data integrity by allowing for a comparison of the data entered, to identify inconsistencies between the two databases and to verify the correct data points by reviewing the hard copy surveys. This will be done prior to data analysis commencing.

REDCap surveys: As described earlier, patients might access the survey and complete consent and the study measures by using the REDCap survey link. If patients have not responded to the initial patient contact and completed the consent and survey within 2 weeks, two reminders will be sent by phone, email, or text messaging.

b). Follow-up Questionnaire (Time 2):
After one month, the patient will receive a follow-up survey via REDCap consisting of the study measures. Patients might also choose to set up an appointment with the PI to meet them at the health center to complete the questionnaire via iPad or hard-copy questionnaire. Additionally, they may choose to complete this survey as a paper copy and return it to the PI in a return stamped envelope the PI will provide to the patient. The PI can also call the patient by telephone, read the questions aloud and record their answers within REDCap on the PI's iPad. Lastly, the PI will also consider meeting the patient at a public location if the patient prefers. These additional follow-up surveys will be kept in a locked file cabinet at the health center along with the other study documents which will only be accessible to the PI. If patients have not completed the follow-up survey within 10 days of the one-month follow-up date, two reminders will be sent by phone, email, or text messaging.

Once patient recruitment ceases, the survey will be closed. The de-identified data will be downloaded from REDCap and stored on a password protected computer. Dr. Mary Dietrich, the PI, and Dr. Stolldorf (faculty advisor) will be the only persons with access to the data. The data will be cleaned and prepared for data analysis.

Patient incentives: At the completion of the baseline survey and app set up for intervention group patients and baseline survey and review of medication list for wait-list control patients, both groups will be given a $25.00 gift card to compensate them for their time and effort in reviewing the medication list, using the app, entering key information and completing the surveys. Upon completion of the follow-up survey, both intervention group and wait-list control patients will receive an additional $35.00 gift card for their time.

Survey Study Measures:
Patients will complete two surveys, representing medication and refill adherence and self-efficacy for appropriate medication use, medication knowledge and medication social support and the first will also gather demographic information. At the end of the study, the follow-up survey will gather information regarding the patient's feedback regarding the smartphone app or use of the printed out medication list. These surveys will take approximately five to ten minutes to complete.
1. Medication and Refill Adherence: Patients will complete the Adherence to Refills and Medications Scale (ARMS) to measure both medication and refill adherence. The ARMS is a global (continuous) 12-item scale, with a possible score of 12-48, patients with low ARMS scores indicate better adherence, it is valid and reliable in a low-literacy chronic disease population. Subscales include taking medications as prescribed (8 items) and refilling

medications on schedule (4 items). Responses range from 1 (none) to 4 (all of the time). Overall internal consistency has been established at Cronbach's alpha = 0.814.

2. Self-efficacy for Appropriate Medication Use: Patients will complete the Self-efficacy for Appropriate Medication Use Scale (SEAMS) to measure self-efficacy for medication adherence. It is a global (continuous) 13-item scale, with a possible score of 13-39. Patients with higher scores indicate higher levels of self-efficacy for medication adherence. It is valid and reliable in low-literacy chronic disease populations. Patients are asked their level of confidence about taking medications correctly. Responses range from 1 (not confident) to 3 (very confident). Overall internal consistency has been established at Cronbach's alpha = 0.89.

3. Medication Knowledge: Patients will complete the Okere-Renier Survey Medication Knowledge Subscale to measure medication knowledge. It is a global (continuous) 5-item scale with responses ranging from (1) strongly disagree to (5) strongly agree. A mean score is then calculated. Scores range from 5-25 with higher scores indicating greater medication knowledge. Overall internal consistency has been established at Cronbach's alpha = 0.83.

4. Medication Social Support: The measurement named Social Support: Medication-specific, consists of 8 items ranging from (0) never to (4) very often. It is a continuous measure, and a mean score is calculated. Higher scores reflect more medication support. Overall internal consistency has been established at Cronbach's alpha = 0.92.

5. Intervention process (intervention group only): Feedback about the smartphone app and additional features as well as an open-ended question will be a part of the second survey to ascertain opportunities and challenges of using the smartphone app and describe aspects of the app, they found most useful and least useful. Survey questions were developed and tested specifically for this purpose during the pilot study for use in this RCT. Patients will be asked if they plan to continue using the app after study completion.

6. Hard copy medication list (wait list control group only): Feedback about the usefulness of the hard copy medication list will be obtained at the end of the study.

2.) Chart Extraction:

The medication list from the patient's EMR will be provided by the patient. This printed-out medication list will be used to a) obtain name, medical record number (MRN) and date of birth (DOB) to establish identity and be validated by the patient and b) to confirm with the patient medications to be entered into the app. If there are any discrepancies between what the patient says they are taking and what is listed on their medication list, the PI will consult with the patient directly. All identifying information on the printed-out copy of the medication list will be blacked out and replaced by the patient's REDCap Record ID. The medication list and the flyer/referral form will be kept in a locked file cabinet in the health center.

3.) Behavioral Observation:

While the patients are entering their medication information, the PI will be observing and recording on a checklist developed by the PI for this purpose the following: a) if the patient had difficulty visualizing the app; b) if they had difficulty with dexterity while using the app, and c) how many times the patient's input of medications needed to be corrected when entering their medications. The length of time from starting to download the app to completing set-up and

reviewing the app will also be recorded. The observation will occur once and will be recorded on a checklist by the PI while the patient is setting up the app with the help of the PI.

D) RANDOMIZATION

Once patients complete the baseline survey, patients will be randomized within each site to help reduce the likelihood of site bias. Patients will be randomized to either a wait list control group or the app intervention group. Randomization will be done by the PI automatically through REDCap. Intervention group patients will use the medication adherence app for 1-month and wait-list control group patients will receive a printed out copy of their medication list and have the name, dose, frequency and indication for their medications reviewed verbally with them by the PI. Both the intervention and wait-list control group will be contacted within the first week of enrolling in the study to see if they have any questions regarding the app or their medications in the case of the wait-list control. The follow-up measures will be completed by study patients in both the intervention and the wait-list control groups. At study completion, those randomized to the wait-list control group will be offered assistance by the PI to set up and use the app.

E) INTERVENTION

1.Intervention Group: The PI will assist the patient to download and set up the free Medisafe app on their smartphone at the clinic. The PI will use a unique URL, which can be texted or emailed to the patient, to facilitate the patient download of the HIPAA compliant app on their mobile smartphone. The PI will educate patients on how to use the app using educational materials developed for the study by the PI. The PI will also show patients the App "Help & Support" page, which answers commonly asked questions. This will be referred to as a "tutorial session." Fidelity will be enhanced through the use of a "Checklist for App Set-Up" developed by the PI for the study to guide the App set-up process. The checklist with the patient record ID will be stored with the other study documents.

The following steps will be taken by the PI in this tutorial session:

1) Guide the patient with downloading the app to their phone.

2) Once the download is completed, the medication list, extracted from the chart, can be entered.

- Show patients how to enter the medication name, dosage, medication appearance (color and format of pill), frequency (every day, every other day, specific days of the week, etc.), the time the medication is regularly taken, and the number of pills left for the refill reminder (if the patient wants that option).
- If patients are having difficulty entering their medications, demonstrate the process by entering one of their prescribed medications. This will ensure the patient understands how to enter medications in the app.
- After the scheduled medications are added, show the patients how to access their list of medications in the app and how to edit a medication that was already in their list, e.g., change the medication dosage.

- In addition, for some of the medications already in the app's database, show the patient how to access information about the specific medication, including written information and a video about what the medication is for, what it may interact with, side effects etc.

3) Patients can choose what language they would like to use when using the App by toggling to the desired language.

4) Show the patient how to indicate that the medication was taken, skipped or rescheduled when they receive a reminder alarm to take their medication.

5) Introduce patients to additional app features including:

a) Reports: how to check their weekly adherence report in which their adherence was calculated based on the number of times they clicked that the medications were taken.

b) Medfriend: how to invite a family member or friend to be a Medfriend in the app. This process entails the patient adding the family members/friend's contact information in the form of a cell phone number and email and inviting them to download the app and obtain access to the patient's medication list and then they will receive an alert if the patient misses a scheduled medication dose.

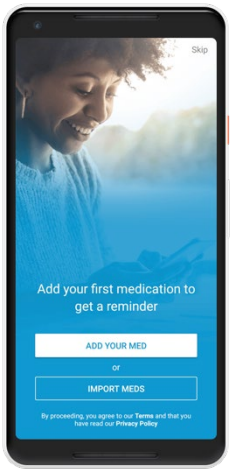
c) Under settings, how to set Medtones, snooze time, receive a morning reminder to take their medications with them and change the home screen style.

d) How to access the help and support section.

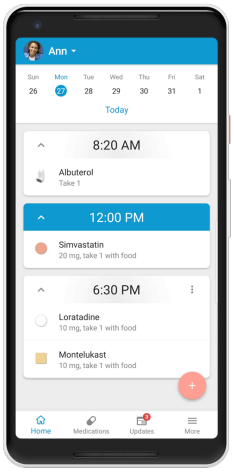
The patient will be given the PI's contact information in case of any questions or concerns. The PI will follow up with the patient through text, email or phone call (whichever the patient prefers). This preference will be noted on the flyer/referral form as well as in an instrument entitled Subject Information in REDCap.

2. Wait-list Control Group: The wait-list control group patients will receive a printed out copy of their medication list and have the name, dose, frequency and indication for their medications and reviewed by the PI. They will be contacted within the first week of enrolling in the study to see if they have any questions regarding their medications. The follow-up measures will be completed by study patients in both the intervention and the wait-list control groups and feedback on the usefulness of the printed-out medication list and ways they used it to facilitate medication management. At study completion, The PI would make available the use of the app and will assist patients in setting up the app, as described above.

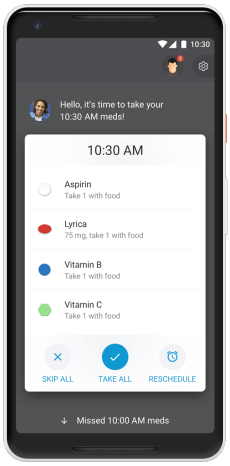
Screenshots of Android Screens:



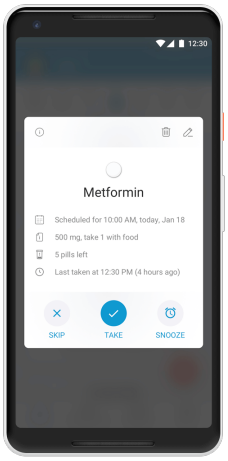
Adding med



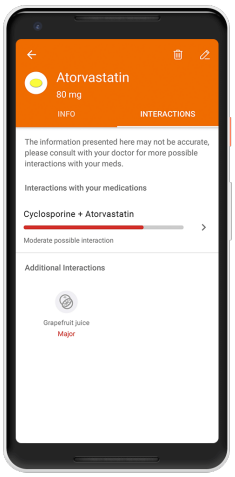
Daily overview timeline



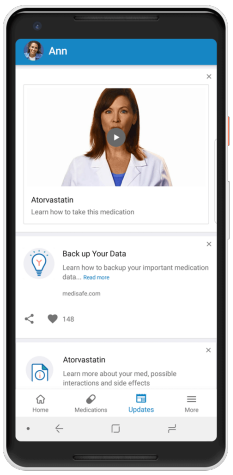
Med reminder



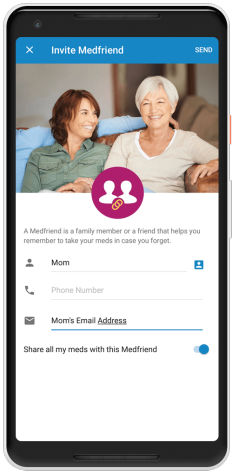
Take dialog



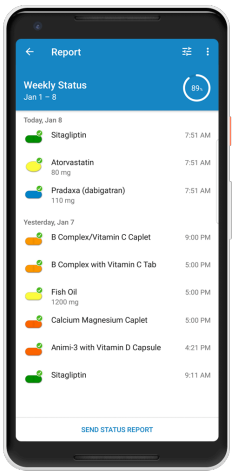
Drug interactions



Updates feed

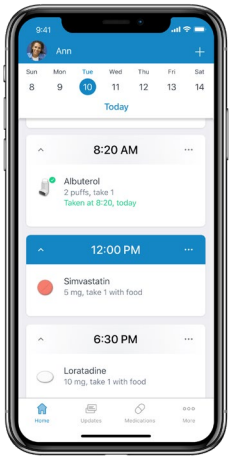


Medfriend

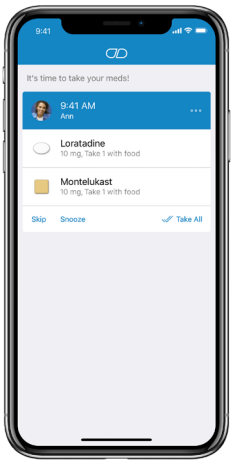


Status report

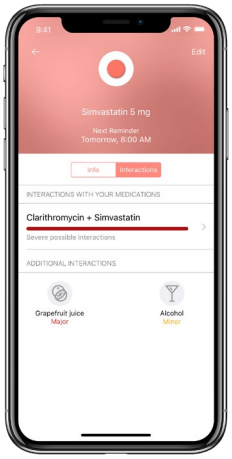
<u>Screenshots of iOS Screens:</u>



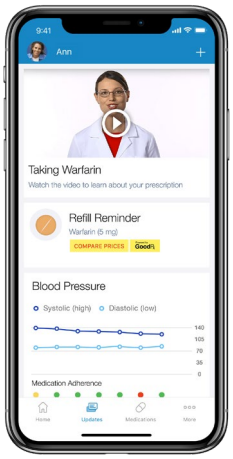
Daily overview



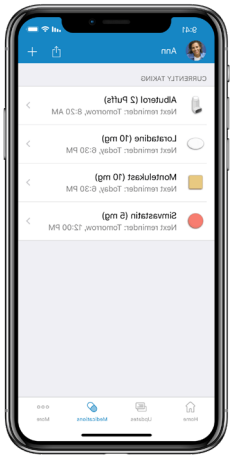
Med reminder



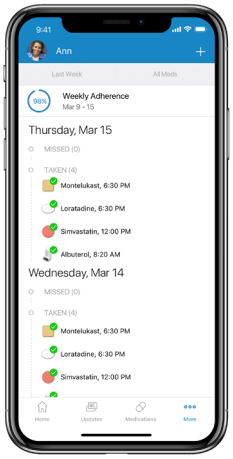
Drug interactions



Updates feed



Med cabinet



Status report

F. DATA ANALYSIS

IBM SPSS Statistics will be used for the quantitative summarization of the effects of the use of the app on the change in self-efficacy (SEAMS) and medication adherence (ARMS) from baseline to 1-month. Descriptive statistics will summarize sample characteristics and study measures. Raw change values from T1 to T2 in the adherence (ARMS), self-efficacy (SEAMS), medication social support, and medication knowledge scores will be calculated. Tests on the effects of the Medisafe app on those outcome measures will be conducted using multiple linear regression models. Given measurement error inherent in self-report measures, a reliable change index (RCI) criterium will be generated for each self-report measure. Each patient's raw change value will be evaluated against that criterium to determine whether the change was reliable or not and the direction of that change.