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Date: Thursday, October 5, 2017 3:10:44 PM Print Close

IRB_00071714 **Created:** 2/12/2014 10:55 AM View: 4. Study Information

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Title: Use of a Smartphone Medication Reminder Application to Promote Adherence to Oral Medications by Adolescents and Young Adults with Cancer

4. Study Information

1. **Design of Study (select all that apply):**
   Survey/Questionnaire Research
   Observational Research
   Prospective Clinical Research
   If Other, describe:

2. **Does your study involve the use of any placebo?**
   ○ Yes ● **No**

3. **Length of entire study, from initiation through closeout:** 2 years

4. **How will participants be recruited or identified for inclusion in the study?**

   a. **Select all methods that will be used:**

   In-person contact (e.g., patients, students, etc.)

   Referrals

   Written or electronic record review

   Written advertising (flyers, brochures, website postings, newspaper ads, etc.)

   From a database or participant pool for which participants have given prior permission to be contacted for research studies

   b. **Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):**

   Participants will be recruited in the following ways:

   1)The clinical research assistant (CRA) for the study will conduct a daily review of the list of oncology patients at Huntsman Cancer Institute, Primary Children's Hospital, and the University of Utah Hospital to identify those meeting the age and treatment inclusion criteria. A HIPAA waiver of authorization is requested from the Institutional Review Board, as it poses minimal risk to patient privacy and is essential for identification of eligible patients. Upon identifying an eligible patient, the CRA will verify with a member of the oncology team (e.g., patient's physician, nurse, physician assistant) that the patient meets the inclusion criteria. If the patient is deemed eligible by the treatment team, the CRA will request permission to approach the patient during the clinic appointment to discuss the study.

   2) Flyers will be distributed throughout Huntsman Cancer Institute, Primary Children's Hospital and the University of Utah hospitals to advertise the study (see flyers attached). If patients self-refer in response to advertisements, they will be provided information from the CRA. The CRA will verify patient eligibility with the patient, via the medical record, and with the patient's treatment team.

3) Participants who are seen at Primary Children's Hospital or Huntsman Cancer Institute who are identified as potentially eligible for the study may also be recruited using a letter from their medical provider that introduces the study and states that survivors may receive further contact from researchers) about the study. (See recruitment letter attached).

4) If the CRA is not present at a clinic appointment or when a patient is inpatient, the provider will briefly discuss the study and use a referral form to obtain contact information of the patient, if the patient is interested in learning more about the study (see provider referral form attached). The CRA will follow-up with the patient.

5) Information about the Yamazon study will be available on the Huntsman Cancer Institute webpage (www.http://healthcare.utah.edu/hunstmancancerinstitute/research/research-projects/yamazon-project.php) and via social media postings (see advertisements attached). Patients who self-refer in response to these advertisements will receive a follow-up from the study team. Internet and social networking postings will occur through the following organizations: Utah Cancer Action Network (www.ucan.cc/), A Quality Life Community (www.aqualitylife.org/); HappyChemo (www.happychemo.com); Utah Cancer Foundation (utahcancerfoundation.com); Cancer Wellness House (www.cancer-wellness.org).

5. How will consent be obtained?

Informed Consent Process (with or without a document)

6. Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.

Enrollment:

Potential participants who are deemed eligible based on chart review and consultation with the medical team will be enrolled into the study in conjunction with the patient's clinic appointments. After obtaining permission from the oncology team to approach the patient (and parent if patient less than 18 years), the CRA will ask the patient/family of their interest in learning more about the study. Patients (and parents if applicable) will be approached in a private room in the inpatient oncology unit or the outpatient oncology clinic. The CRA will provide information about the study and administer the screening questionnaire to further assess eligibility regarding smartphone ownership (iPhone, iPad, or iTouch running iOS 5.0 or later or Android device running OS 2.1), willingness to use a smartphone medication reminder application (Dosecast version 8.0.5 or most current version), and prior use of such an application. If a CRA is unavailable to recruit a patient, a member of the oncology team will provide brief information about the study and will provide the patient with a referral form. Patients who complete a referral will be contacted after their appointment and study enrollment will occur at their future clinic appointment.

Although enrollment can occur in both an outpatient and inpatient setting, study visits will only occur after a patient has been discharged and is receiving their care on an outpatient basis. The CRA will track and record the times that participants are in an inpatient setting. This data will be monitored in a password-protected tracking log.

If eligible patients do not decline participation but request more time to consider participation, the research team member will re-contact them within 1 week of the initial meeting to enable them to consent/assent or decline. Eligible patients (and parents if applicable) who decline study participation will be asked to select reasons for refusal from a pre-developed list of potential reasons for refusal. A confidential list of patients (and parents if applicable) who have been approached but not enrolled in the study will be maintained by the CRA to ensure that no patient is approached more than once. The number of patients approached, number eligible, number enrolled and reasons for refusal will be recorded. The study team will maintain a password protected tracking log for patients approached about the study. This list will be monitored for recruitment and recruitment outcomes. In addition, The study team will maintain a password-protected tracking log of all patients enrolled in the study to monitor patient's progress through the study procedures

Questionnaires:

Participants will be emailed a link weekly to complete questionnaires online using REDCap. This link will connect to a REDCap survey. This will be a secure website for participants to take their weekly surveys. If questionnaires are not completed within 24 hours, a reminder email will be sent, and if still not completed at 48 hours, another reminder email will be sent. If a participant misses a week of REDCap questionnaire completion, the study team will conduct follow-up phone calls, text messages, or emails to increase completion rate of the questionnaires and minimize missing data. Estimated time to complete questionnaires can be found in the Measures Timetable (uploaded to the application).

Perceived behavioral control for adherence to oral medications and intention to adhere to oral medications will be measured using items and scaling as recommended by Ajzen & Fishbein (1980) and modeled on those used by Hagger,

Chatzisarantis, & Biddle, 2001; Keats, Culos-Reed, Courneya, & McBride, 2007; Mummery, Spence & Hudec, 2000; and Sheeran, Conner, & Norman, 2001. Perceived behavioral control will be measured with 6 items using 5-point scales. Intention will be measured with 2 items using 5-point scales. Self-reported adherence behavior will be measured with 1 multiple choice and 2 open-ended items. These items identify the percentage of time that the participant was adherent over the past week, the number of missed doses in the past week, and reasons for non-adherence. Self-reported smartphone medication reminder application use will be measured with 10 multiple choice items.

Self-reported adherence behavior will additionally be measured with the 8-item Morisky Medication Adherence Scale (MMAS-8), which assesses specific medication-taking behaviors and determinants of adherence behavior (Morisky, 2008). The MMAS-8 has 7 items using a yes/no dichotomous response option and one item measured using a 5-point scale. Allocation of treatment responsibility will be measured with 38 items using a 4-point scale (Pai et al., 2010). Constructs from the Theory of Planned Behavior including attitude, perceived behavioral control, subjective norms, intentions, and past behavior will be measured using items developed by Chisholm et al (2007). The questionnaire includes 23 multiple choice items. Self-Efficacy will be measured using the Medication Adherence Self-Efficacy Scale-Revised (MASES-R) scale (Fernandez et al., 2008). The 13 items included in the MASES-R are measured using a 4-point scale. The cognitive representation of medicine will be measured using the Beliefs about Medication Questionnaire (BMQ)-Specific developed by Horne (1999). This questionnaire uses 18 items using a 5-point scale. Barriers to medication adherence will be measured with the Adolescent Medication Barriers Scale (AMBS) developed by Simons and Blount (2007). This questionnaire uses 16 items using a 5-point scale and one open ended question to allow the participant to elaborate on their responses. The feasibility and acceptability of smartphone medication reminder application use will be measured with 21 items. These items, based on constructs included in the Technology Acceptance Model (Venkatesh & Bala, 2008) include those used in a previous study evaluating the feasibility and acceptability of a mobile symptom assessment application (Macpherson et al., 2014) and are supplemented with investigator-designed items. Psychological factors will be measured using the Brief Symptom Inventory 18 (BSI-18) (Derogatis). This questionnaire uses 18 items using a 5-point scale assesses somatization, depression and anxiety. Demographic factors will be measured using 15 items recommended by the Behavioral Risk Factor Surveillance System (BRFSS, 2014).

Study visits:

Visit 1: After enrollment, the participant will receive EDM (Electronic Data Monitoring) caps for up to six scheduled medications that they are receiving. A manual pill count will be completed for this visit either in clinic or via telephone. If the participant has their medications with them at Visit 1, the manual pill count will be completed by the study team pharmacist, pharmacy student, or a member of the research team in clinic. The study staff completing manual pill counts will complete hazardous drug safe handling training prior to contact with patient medication. If the participant does not have their medications with them at Visit 1, the study team will arrange a time to call the participant to complete the manual pill count over the telephone.

Visit 2: After completion of week 4, participants will have an outpatient study visit for: 1) EDM cap data download and manual pill count. The study staff will either call, text, or email the participant prior to Visit 2 to remind them to bring their medications and eCAPs to Visit 2 for EDM cap data download and manual pill count. A manual pill count will be completed for this visit either in clinic or via telephone. If the participant has their medications with them at Visit 2, the manual pill count will be completed by the study team pharmacist, pharmacy student, or a member of the research team in clinic. The study staff completing manual pill counts will complete hazardous drug safe handling training prior to contact with patient medication. If the participant does not have their medications with them at Visit 2, the study team will arrange a time to call the participant to complete the manual pill count over the telephone. Participants, however, will be encouraged to bring their pill bottles with them to this visit. 2) To download Dosecast program and receive instruction in smartphone medication reminder application use by the CRA. Each participant will be given an individual passcode that will allow Montuno Software to identify app usage and to share data with the study team. Participants will not enter any personally identifiable information into the app, and no PHI will be shared with Montuno Software. 3) If a participant does not attend the in-person Visit 2 (Week 4), there will be an option to mail, email, or send via RedCAP the questionnaire that would have been completed at that visit. If the participant does not attend the in-person Visit 2 (Week 4), the initiation of the Weeks 5-12 questionnaires will be deferred until the participant has downloaded the Dosecast app, set up the reminders, and received instruction on its use.

Visit 3: After completion of week 12, participants will have a final study visit in an outpatient setting for EDM cap data download and manual pill count. The study staff will either call, text, or email the participant prior to Visit 3 to remind them to bring their medications and eCAPs to Visit 2 for EDM cap data download and manual pill count. A manual pill count will be completed for this visit either in clinic or via telephone. If the participant has their medications with them at Visit 3, the manual pill count will be completed by the study team pharmacist, pharmacy student, or a member of the research team in clinic. The study staff completing manual pill counts will complete hazardous drug safe handling training prior to contact with patient medication. If the participant does not have their medications with them at Visit 3, the study team will arrange a time to call the participant to complete the manual pill count over the telephone. Participants, however, will be encouraged to bring their pill bottles with them to this visit. If a participant does not attend the in-person Visit 3 (Week 12), there will be an option to mail, email, or send via RedCAP the questionnaire that would have been completed at that visit.

Estimated time to complete questionnaires can be found in the Measures Timetable (uploaded to the application).

Phone calls, emails, and/or text messages will be used to follow-up about other study procedures as needed.

Dosecast Application use:

Montuno Software will be issuing to study staff a pool of unique, randomly-generated patient credentials, each of which will be distributed to a study participant. The study participant will be instructed to download and install the free Dosecast

app from the Apple or Google app store and enter the provided credentials upon first use. As participants use the app, their adherence data will be silently collected by the app and securely and automatically uploaded to Montuno's cloud servers. Data will be downloaded by the CRA from Montuno's cloud servers regarding amount and nature of use of smartphone application by participants.

Data storage and analysis:

We will enter in all data, including PHI, into a secure site (i.e., the REDCap system) here at the University of Utah. REDCap features include differentiated user roles and privileges, user authentication and authorization security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes. De-identified data will be downloaded from REDCap onto University of Utah, secure servers and will be accessed using encrypted, password-protected computers.

Montuno Software will extract the adherence data from Dosecast corresponding to all the credentials used by study participants and publish the data on a password-protected FTP site for study administrators to download. Data will be removed from the FTP site 1 week after publishing and the data has been downloaded by the CRA. This data will also be stored on University of Utah, secure servers and will be accessed using encrypted, password-protected computers.

The PI will work with external investigators (see external investigators) who will assist with data analysis. The PI will only share a limited, de-identified dataset with the external investigators. This limited dataset will not include PHI. In order to ensure that PHI has been completely removed from this dataset, the CRA will remove all identifiers from the data and the PI will verify at all identifiers have been removed before data is shared with the external investigators.

7. Are all procedures for research purposes only (non-standard or non-standard of care procedures)?

● **Yes** ○ No

If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

8. Is there a safety monitoring plan for this study?

○ Yes ● **No**

9. Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.

To explore the feasibility and acceptability of using a smartphone medication reminder application to promote adherence to oral medications and to characterize application use.

We anticipate enrolling at least 25 participants for this pilot study of medication reminder application feasibility and acceptability. Eligibility, enrollment and retention rates will be estimable with 95% confidence intervals ranging in width from 20% (for estimates near 5% or 95%) to 40% (for estimates near 50%).

Change in adherence behavior will be assessed pre-intervention (end of week 4) and post-intervention (end of week 12) based on (1) one self-reported multiple-choice question and 8 questions in the Morisky Medication Adherence Scale (MMAS-8); (2) EDM cap count; and (3) manual pill count. Pre-intervention and post-intervention self-reported adherence behavior will be compared, and the proportion of participants reporting higher adherence post-intervention, as well as associated 95% confidence intervals, will be calculated overall and by intensity of medication regimen. Rates of medication adherence pre-intervention (weeks 1 through 4) and post-intervention (weeks 5 through 12) will be calculated based on EDM cap count and manual pill count separately by dividing observed pill count by expected pill count. Expected pill count will be determined based on the participant's prescribed oral medication regimen. Paired differences in adherence rates (post-intervention minus pre-intervention) based on EDM and manual counts, respectively, will be generated for each participant, and mean change and associated 95% confidence intervals will be calculated. To evaluate the association between self-reported adherence behavior and adherence behavior measured by EDM caps and manual pill counts, EDM caps and manual pill count estimates will be reoperationalized as ordinal levels corresponding to the ordinal levels used in the self-report measure of adherence behavior. Cohen's kappa, an estimate of rating agreement, will then be calculated. We will summarize participants' perspectives on feasibility and acceptability using the feasibility and acceptability questionnaire.

Overall indices of all potential predictors of adherence (i.e., allocation of treatment responsibility, attitudes towards medications, perceived behavioral control for adherence, subjective norms, intention to adhere, past adherence behavior, self-efficacy, cognitive representation of medicine, barriers to adherence, psychological symptoms, demographic factors) will be calculated. We will summarize mean levels of these potential predictors at all timepoints available and will calculate mean change in these predictors over time. We will use regression-based analyses to examine the potential impact of these predictors prior to use of the SmartPhone app on adherence. We will also explore associations between

changes in these predictors and changes in adherence. For example, we will explore whether increased self-efficacy is associated with improved medication adherence.

We will further conduct a series of analyses to examine the relationship between potential predictors of adherence and intervention outcomes. Models will be adjusted for within-subject correlation associated with repeated measurement.

Association of potential predictors of adherence with adherence to oral medications. We will fit a GEE model with potential predictors as the independent variable perceived behavioral control and dependent variable adherence behavior (from EDM caps and manual pill counts, respectively), adjusted for pre-/post-intervention, accounting for within subject correlation.

Sensitivity analyses will be conducted to assess the robustness of analytic conclusions when pre-intervention and post-intervention measures are analyzed separately; and accounting for intensity of medication regimen.

Missing Outcome Data:

We anticipate three mechanisms by which data may be missing in this study: non-compliance, withdrawal and inpatient care. Missing data will be summarized descriptively. Potential associations of missingness due to non-adherence or withdrawal with demographic factors and prior medication reminder application usage will be explored. For this study, participants who withdraw prior to beginning the intervention will be excluded from analyses of the Secondary Aims. We will reduce the analytic impact of missing data by pre-summarizing outcome measures across the pre-intervention interval (weeks 1 through 4) and separately across the post-intervention interval (weeks 5 through 12). For calculation of means and proportions, only non-missing observations will be included in the denominator. In addition, we will perform a series of sensitivity analyses in which we will substitute the worst-case outcome for those observations that are missing due to non-adherence or withdrawal.