Development and Pilot Randomized Control Trial (RCT) of a Text Message Intervention to Facilitate Secure Storage and Disposal of Prescription Opioids to Prevent Diversion and Misuse: Phase 2

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Study Title: Development and Pilot Randomized Control Trial (RCT) of a Text Message Intervention to Facilitate Secure Storage and Disposal of Prescription Opioids to Prevent Diversion and Misuse: Phase 2

Short Title: Opioid SMS R34 Phase 2

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Background, Rationale and Context

Drug overdoses are now the leading cause of injury-related death in the United States (US), 35% of which are due to nonmedical use of a prescribed opioid (Scholl, 2019). In the US, 3.3 million people aged 12 or older report past 30-day nonmedical prescription opioid use (NMPOU), defined as use of a prescribed opioid analgesic without a prescription or for reasons other than prescribed (SAMHSA, 2019). The existing supply of opioid analgesics is high; in 2017, the prescribing rate was 58.7 opioid prescriptions per 100 persons (CDC, 2018). Many of these opioid analgesics are leftover following treatment (Maughan et al., 2016) and kept in homes rather than being disposed after ceasing use or expiration (Kennedy-Hendricks et al., 2016). Over half of individuals who report NMPOU obtain prescription medications from a relative or friend, with or without their knowledge (Cranford et al., 2008; SAMHSA, 2019). Thus, diversion of excess medication is the primary source of NMPOU. Secure storage and disposal of unused opioid analgesics have been extensively promoted at the federal level and adopted by local communities as a strategy to combat diversion of NMPOU. The premise underlying these two strategies is that (1) secure storage minimizes the likelihood of diversion while opioid analgesics are being used during treatment and (2) disposal programs provide opportunities for patients to remove unused or expired opioids outside the home, ultimately reducing availability for NMPOU. However, recent evidence demonstrates that a majority of individuals do not securely store opioids analgesics (Bicket et al., 2018) and only a fraction of unused prescription opioids are disposed of through disposal programs (Egan et al. 2016). This is likely due, in part, to a widespread failure of knowledge about and lack of motivation to securely storing and disposing unused prescription opioids. There is evidence that increasing awareness of storage procedures and disposal mechanisms (K. L. Egan et al., 2019; Yanovitzky, 2016) and targeted interventions delivered by healthcare systems may enhance secure storage and disposal of opioid medications (e.g., Hasak et al., 2018; Maughan et al., 2016). Mobile phone text message reminders, a technology used to prompt multiple health behaviors (Biederman et al., 2019; Richman et al., 2016), may address the need to provide timely guidance on proper handling of opioid medications by prompting patients to securely store and dispose unused prescription opioids.

Objectives

The overall objective of this R34 application is to test the feasibility of a novel, evidence-informed strategy that utilizes a persuasive, informational text message reminder system to expand the impact of secure storage and disposal programs. Our central hypothesis is that implementation of a text message intervention will increase secure storage of opioid analgesics during treatment and disposal following treatment.

This protocol will cover:

Aim 2: Pilot test a SMS text message intervention to facilitate secure storage and disposal of unused opioid analgesics using a randomized control trial (RCT).

Overall Research Design

This protocol is specific to the randomized control trial (RCT) that will be completed under Aim 2. To assess the efficacy of the intervention, we propose to conduct a RCT. Participants will be randomized into one of two groups: (1)

intervention or (2) control group. The Intervention will consist of a series of text messages about secure storage and disposal of their prescribed opioid medication.

Recruitment

We will use a multimethod approach to recruiting participants for the RCT:

1) **Atrium Health Wake Forest Baptist MyChart.** We will recruit participants using Atrium Health Wake Forest Baptist MyChart. Study information will be sent to patients who meet the eligibility criteria. The following message will be sent:

   Message Header:

   Research Opportunity: Medication Safety Study
   Principal Investigator: Kathleen Egan, PhD

   Message Body:

   My name is Dr. Kathleen Egan. I am an Associate Professor with Wake Forest University School of Medicine. Our team is seeking volunteers to participate in a research study related to having prescribed pain medication in the home.

   You may be eligible to participate if you:
   - *Are 18 years of age or older*
   - *Own a cell phone with the capability of receiving SMS text messages*
   - *Received an opioid prescription within the past 14 days*

   What you will be asked to do:
   - *Answer some questions about your medical history*
   - *Complete 3 brief surveys online*
   - *Receive text messages to your cell phone approximately 1-2 times per week for about 7 weeks*

   If you qualify and complete the study requirements, you will receive up to $75 to thank you for your time.

   If you would like to learn more about the study, please visit the following website [insert link to study website/consent form] OR contact the study team at [insert study coordinator phone #] or [email].

   Kathleen Egan, PhD
   Department of Implementation Science
   Wake Forest University School of Medicine

   Wake Forest University School of Medicine is the academic core of Atrium Health

2) **East Carolina University (ECU) Physicians Pharmacy.** We will collaborate with East Carolina University (ECU) Physicians Pharmacy to recruit participants (see letter). Pharmacists will hand out flyers to patients who have been dispensed opioid medication and study materials will be posted in the pharmacy.
3) **Advocate/Atrium Health/Wake Forest Baptist Pharmacies.** Study materials will be posted in pharmacies where prohibited.

SMS Text Intervention

Participants in the intervention group will receive a series of text messages to securely store prescription opioids during treatment and dispose of unused prescription opioids. Twillio will be used to deliver text messages to participants. Twilio

is a third-party web service that integrates with REDCap, allowing users to send survey invitations and alerts/notifications to participants as SMS text messages or voice calls. It acts as a conduit between participants' mobile devices and your REDCap project.

The intervention will last 45 days and will start immediately following completion of the baseline survey. All participants will receive seven identical SMS text messages over the course of the intervention. Participants will receive four SMS text messages about storing their medications prior to the midpoint survey which will take place on Day 25 of the research study. SMS text messages about disposal of unused medications will begin after Day 31 of the intervention to ensure that all participants would have completed their treatment regimen. We expect that a 30-day prescription is the maximum and this will be confirmed with data provided at the baseline survey. If someone has more than a 30-day prescription, they will not be eligible to participate in the study. Participants will receive three SMS text messages about disposing of their unused medications prior to the post intervention survey which will take place on Day 45 of the research study. Participants will receive 1-2 SMS text messages about storing and disposing of their unused medications per week which reflects participant feedback from the Qualtrics survey completed in Phase 1. The order in which all SMS text messages are delivered will be randomized.

The SMS text messages that will be delivered (Table 1) were developed in Phase 1 of this study. Community members who reflected the inclusion criteria for the RCT informed the development of the text messages through focus group discussions and a cross-sectional forced exposure survey. The recommendations for storing medications have been endorsed by the CDC and recommendations for disposal are currently endorsed by the Food and Drug Administration.

Table 1. Participant Derived Text Messages

Storage Messages

1) It is your prescription, not theirs. Keep your medication hidden and out of reach.
2) Locking up your prescription pain pills could save a life. Keep them in a locked location such as a cabinet or box.
3) Your favorite hiding spot could save a life. Keep your pain pills where someone would not look for them.
4) Your prescription can become someone else's addiction. Lock up your pain pills.

Disposal messages

1) Dispose of your unused medications. You may save the life of someone you love. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
2) Discarding your unused pain pills could save a life. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
3) Your prescription can become someone else's addiction. Safely discard unused or expired medications. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.

We will not be including information about opting out of receiving text messages in each text message as opting out of a text message will remove them from the entire study (evaluations are being sent via sms text messages as well). To minimize confusion and unintentional removal from the entire study, we will be providing opt out language in the consent form along with a broader description of the implications of opting out of receiving text messages: *"To opt out of receiving text messages, reply STOP to a text message. If you choose to opt of receiving a text message by replying STOP, you are also choosing to end all participation in this research study and will not be able to rejoin the study."*

Control Study Condition. Individuals who are assigned to the study condition will be invited to take the midpoint and post intervention survey. Immediately after completing the post intervention survey, participants will receive information on ways to securely store and dispose of unused opioid medication. This information will be provided in the REDCap® survey.

Study Population

We aim to recruit 436 participants.

Inclusion criteria include being (1) 18 years of age or older, (2) able to read and speak English, (3) owning a cell phone with the capability of receiving SMS text messages, (4) within 14 days of receiving their prescription, and (5) having an opioid prescription that is for 30 days or less.

Exclusion criteria include being (1) 17 years of age or younger, (2) not able to read and speak English, (3) not owning a cell phone with the capability of receiving SMS text messages, (4) 15 days or more after receiving their prescription, and (5) having an opioid prescription that is for 31 days or greater.

Randomization

Simple randomization to study condition is an appropriate approach to achieve equal groups given our sample size exceeds 100 (Kim & Shin, 2014). Prior to recruitment, a random number generator in SPSS will be used to create an allocation table to assign participants to study conditions. After the table has been generated, it will be uploaded into the REDCap® Randomization Module. Once a participant completes the baseline survey, the Randomization Module in REDCap® will randomize participants to study condition based on predefined allocation table.

Study Endpoints

Data collection will end after 436 participants have been enrolled in the study. Enrollment will be defined as completion of the baseline survey.

Evaluation Design, Measures, and Statistical Plan

Process Evaluation. To assess critical process evaluation data on intervention fidelity and dose, we will generate descriptive summary statistics of key intervention metrics including, 1) proportion of messages that are delivered, 2) mean and standard deviation calculations for items regarding perceptions of text messages, and 3) proportions of individuals indicating exposure to storage and disposal messages.

Outcome Evaluation. Efficacy of the text message intervention will be assessed with three mobile-optimized web-based surveys. Participants will complete baseline, midpoint (25 days after completing the baseline survey), and a post-intervention (45 days after completing the baseline survey) surveys. The invitation to complete the midpoint and post-intervention surveys will be texted to participants via Twillio+REDCap®, the same program used to deliver the intervention, and the survey will be housed within REDCap®. Up to 2 text reminders with access to the survey will be sent over a one-week period. If the survey has not been completed 3 days after the third invitation has been sent, a research assistant trained in administering telephone questionnaires will call the participant and offer the opportunity to complete the survey over the phone.

Analyses will be conducted to assess group differences on two primary dichotomous outcomes: (1) secure storage of their opioid analgesic (locked vs. unlocked), and (2) disposal of unused medication (disposed vs. did not dispose). We will use a modified intention-to-treat (ITT) design. While an ITT design minimizes bias and Type 1 error, it is often considered a conservative approach that may increase Type 2 error. A modified ITT design allows for the exclusion of some randomized subjects in a justified way to achieve the goal of minimizing both Type 1 and 2 errors. For this study, we will retain the ITT approach by including all participants regardless of their compliance with the text message intervention. We will modify the ITT approach by excluding participants who do not have outcome data since we will not have a mechanism to assess their storage or disposal behaviors which could inflate Type 2 error if retained in analyses. We will first test for group equivalence in demographic and household characteristics of the participant, diagnosis, the procedure that was conducted, and information about the prescribed opioid (e.g., type, number of pills, and duration of treatment). Group differences are not expected in the context of randomization; however, if one of these variables is associated with both condition and an outcome variable, we will include it as a covariate in the prediction of that outcome. Data will be compiled and screened for integrity, outliers, missing values, and violations of the assumptions of logistic regression. Missing values will be handled in regression analyses using full maximum likelihood estimation.

We will use multiple logistic regression to test the main hypotheses that the intervention will be positively associated with secure storage (locked v. unlocked) and disposal (yes v. no) behaviors which will allow us to control for demographic variables known to influence the outcomes. We will use a two-step logistic regression to predict each outcome. In Step 1, demographic variables will be entered into the model. We will retain variables significantly associated with the outcome at $p<.05$. In Step 2, group membership will be entered into the model. In addition to testing the main hypotheses, we will examine disaggregated treatment effects on measured HBM constructs and primary outcomes by key individual characteristics to explore potential differences that could be examined in a further study.

We plan to enroll 436 participants based on assumptions from a RCT utilizing a text intervention that encouraged parents to vaccinate their adolescent child (Rand et al., 2017) and a RCT that assessed the delivery of a deactivation product with educational material by medical staff on self-reported disposal of unused opioids (Lawrence et al., 2019). Power calculations based on proportions of vaccine completion for the group exposed to the text message intervention (0.49) and the unexposed group (0.30) (Rand et al., 2017) indicate a total of 230 participants will be needed to detect a difference in the impact of a text message intervention. Power calculations based on proportions of disposal for the group who received the deactivation product intervention (0.72) and the unexposed group (0.56) (Lawrence et al., 2019), indicate a total of 306 participants will be needed to detect a difference in disposal of unused opioid medications. We based our sample size on more conservative estimates from Lawrence et al., 2019. To account for loss to follow-up (Maughan et al., 2016), we plan to recruit an additional 130 participants for a total of 436 participants.

Adverse and Serious Events

Due to the nature of the study, adverse or serious events as a result of the study are not anticipated. All research staff will be carefully trained to recognize and report to PI Egan any serious, unexpected, or other adverse events. In the event of an adverse or serious event, the PI will notify the WFUSM IRB immediately. If the IRB takes action as a result of an adverse event report or annual review, PI Egan will report these actions to the NIH project officer within 48 hours of her receipt of that information.

Potential benefits to participants and others

There are limited benefits to individual research participants. Research participants will be provided with information on how to securely store and dispose of unused opioid medications as well as contributing to scientific research. This balances well against the minimal risks to participants.

Potential harms to participants and others

There are minimal risks to subjects in this study. Individuals who have been prescribed and dispensed opioid medication and consented to participate in the research study will be randomized to receive a text message intervention or the control condition. The text messages will provide information about secure storage and disposal of unused prescribed opioid medication. In the rare case of a breach of security, there would be the risk of disclosure of identifiable data. Participants in the RCT will receive text messages about best practices for storing and disposing of their prescribed opioids which could be seen by another individual.

Minimization of harms

Discomfort. The text messages have been developed using a multi-phase design with community member input. All measures used in this study are well-validated measures that have been used extensively with this and/or similar populations. Participants will be informed of the types of questions that they will be asked to answer as part of the informed consent process, and they will have the opportunity to skip questionnaire items or discontinue participation in the study at any time without penalty.

Coercion. Participants will be provided with modest compensation for their participation in the study as follows. All participants in the RCT will be provided with incentives following completion of the baseline survey ($25), midpoint survey ($25), and post-intervention survey ($25). The maximum amount of money that a participant may receive for participation in this study is $75.

Confidentiality. We will implement protections to limit any ability to link data with individuals.
Prior to ascertaining desire/consent to participate, we will maintain a spreadsheet stored electronically on a secured device and IRB-approved cloud system that has the name, phone number, and email address of individuals who have met the study criteria. This spreadsheet will include the date we contacted the individual and the way in which we contacted them. The purpose of this spreadsheet is to ensure that they are not invited to participate more times than approved by the IRB. This spreadsheet will also have a unique identifier which will be linked to data pertaining to their prescription number, medication list (i.e., opioid prescription only), age, gender, and race/ethnicity. We will retain this information for use in the event that they consent to participate in the study. These two spreadsheets will be destroyed/deleted once recruitment has closed. ***After ascertaining desire/consent to participate,*** unique identifiers will be assigned to participants – identifiers will be stored separately from the data. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web application for building and managing online surveys, and on a secure and encrypted storage system maintained by WFUSM IT Security. Twillio will be used to deliver text messages to participants. Twilio is a third-party web service that integrates with REDCap, allowing users to send survey invitations and alerts/notifications to participants as SMS text messages or voice calls. It acts as a conduit between participants' mobile devices and your REDCap project.

Alternative treatments or procedures
The alternative is not to participate in the study.

Consent
Potential participants will be directed to the consent form via a weblink or QR code. The consent form will be online in REDCap and potential participants will review the consent without the assistance of a study team member. Potential participants will be directed to the study team if they have any questions. In lieu of a signature, participants will be informed that they should "click 'I agree to participate' at the end of the consent form" to provide their authorization to participate. After consenting to participate, they will be directed to the baseline survey.

The consent form will use language approved by the Wake Forest University School of Medicine IRB that is designed for readability and includes the general topic of the study, the name of the PI, the PI's contact information, the IRB approval number, and the phone number of the Institutional Review Board (IRB) at Wake Forest University School of Medicine. Participants will be reminded that they are not required to answer questions (other than for eligibility), that they can end participation at any time, and that there is no obligation to participate. Given that participants for the RCT may be patients at one of the participating institutions, they will be reminded during the consent process that participation will not impact their treatment or future access to medications. Following completion of the baseline survey, participants will be provided with the consent form and directed to download it or take screenshots of the form.

References
Bicket, M. C., White, E., Pronovost, P. J., Wu, C. L., Yaster, M., & Alexander, G. C. (2018). Opioid Oversupply After Joint and Spine Surgery: A Prospective Cohort Study. *Anesthesia and Analgesia*. https://doi.org/10.1213/ANE.0000000000003364

Biederman, J., Fried, R., DiSalvo, M., Woodworth, K. Y., Biederman, I., Noyes, E., Faraone, S. V., & Perlis, R. H. (2019). A Novel Text Message Intervention to Improve Adherence to Stimulants in Adults With Attention Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*, *39*(4), 351. https://doi.org/10.1097/JCP.0000000000001055

CDC. (2018). *U.S. Opioid Prescribing Rate Maps*. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

Cranford, J. A., McCabe, S. E., Boyd, C. J., Slayden, J., Reed, M. B., Ketchie, J. M., Lange, J. E., & Scott, M. S. (2008). Reasons for nonresponse in a web-based survey of alcohol involvement among first-year college students. *Addict Behav*, *33*(0306-4603 (Print)), 206–210.

Egan, K., Gregory, E., Sparks, M., & Wolfson, M. (2016). From dispensed to disposed: Evaluating the effectiveness of disposal programs through a comparison with prescription drug monitoring program data. *The American Journal of Drug and Alcohol Abuse*.

Egan, K. L., Gregory, E., Wolfson, M., Francisco, V. T., Strack, R. W., Wyrick, D. L., & Perko, M. A. (2019). Disposal of prescription drugs by parents of middle and high school students. *Journal of Child & Adolescent Substance Abuse*, *28*(2), 92–98. https://doi.org/10.1080/1067828X.2019.1590272

Hasak, J. M., Roth Bettlach, C. L., Santosa, K. B., Larson, E. L., Stroud, J., & Mackinnon, S. E. (2018). Empowering Post-Surgical Patients to Improve Opioid Disposal: A Before and After Quality Improvement Study. *Journal of the American College of Surgeons*, *226*(3), 235-240.e3. https://doi.org/10.1016/j.jamcollsurg.2017.11.023

Kennedy-Hendricks, A., Gielen, A., McDonald, E., McGinty, E. E., Shields, W., & Barry, C. L. (2016). Medication Sharing, Storage, and Disposal Practices for Opioid Medications Among US Adults. *JAMA Internal Medicine*, *176*(7), 1027. https://doi.org/10.1001/jamainternmed.2016.2543

Maughan, B. C., Hersh, E. V., Shofer, F. S., Wanner, K. J., Archer, E., Carrasco, L. R., & Rhodes, K. V. (2016). Unused opioid analgesics and drug disposal following outpatient dental surgery: A randomized controlled trial. *Drug and Alcohol Dependence*, *168*, 328–334. https://doi.org/10.1016/j.drugalcdep.2016.08.016

Richman, A. R., Maddy, L., Torres, E., & Goldberg, E. J. (2016). A randomized intervention study to evaluate whether electronic messaging can increase human papillomavirus vaccine completion and knowledge among college students. *Journal of American College Health: J of ACH*, *64*(4), 269–278. https://doi.org/10.1080/07448481.2015.1117466

Rose, P., Sakai, J., Argue, R., Froehlich, K., & Tang, R. (2016). Opioid information pamphlet increases postoperative opioid disposal rates: A before versus after quality improvement study. *Canadian Journal of Anesthesia/Journal Canadien d'anesthésie*, *63*(1), 31–37. https://doi.org/10.1007/s12630-015-0502-0

SAMHSA. (2019). *Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health* (HHS Publication No. PEP19-5068; NSDUH Series H-54)). Center for Behavioral

Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/

Scholl, L. (2019). Drug and Opioid-Involved Overdose Deaths—United States, 2013–2017. *MMWR. Morbidity and Mortality Weekly Report*, *67*. https://doi.org/10.15585/mmwr.mm6751521e1

Yanovitzky, I. (2016). The American Medicine Chest Challenge: Evaluation of a Drug Take-Back and Disposal Campaign. *Journal of Studies on Alcohol and Drugs*, *77*(4), 549–555. https://doi.org/10.15288/jsad.2016.77.549