CLINICAL STUDY PROTOCOL

Determining the Feasibility and Acceptability of a Novel Stigma Resistance Text Message Intervention for People who Use Drugs

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Acceptability of a Novel Text Message Stigma Resistance Intervention for People who Use Drugs

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SYNOPSIS

Primary Objective

We will use an iterative convergent mixed method design[1] to develop and evaluate a stigma resistance text message intervention for PWUD. Text messaging is a scalable and cost-effective modality for health behavior change with demonstrated acceptability and effectiveness in interventions with PWUD, a historically hard-to-reach group.[2–8] Specifically, we aim to:

Aim 1*: Identify PWUD self-stigma subgroups and describe associated demographic, health, and drug use risk factors among rural PWUD in an eight-state multi-site cohort using latent class analysis.*^

Aim 2*: Identify a) stigma-related attitudes and beliefs that are salient to PWUD and amenable to change, and b) text message content and delivery preferences through iterative elicitation interviews with 20 rural Ohio PWUD.*^

Aim 3*: Tailored around findings from Aim 1 and Aim 2, develop an automated daily short message service (SMS) stigma resistance intervention.*^

Aim 4: Evaluate feasibility, acceptability, and preliminary effectiveness of the SMS intervention to increase stigma resistance and reduce self-stigma. We will conduct a pilot trial of the intervention among 30 rural Ohio PWUD in active use and collect quantitative and qualitative data at baseline and four-week follow-up.

Despite wide acknowledgement that stigma is a key barrier to harm reduction and treatment utilization, few studies have intervened on this construct among PWUD in active use. Results of our study will address the current research gap of stigma reduction interventions for PWUD. Our study will further inform whether text messaging is a feasible and acceptable modality for promoting preventive health behaviors in this population.

^ *This study protocol covers Aim 4 only. Aims 1-3 were approved and conducted under separate protocols (UNC IRB# 17-1887 & 18-2747)*.

General Design Description

This Phase 1 study is a single-group feasibility trial of a text message intervention to increase stigma resistance and reduce self-stigma among people who use drugs. All participants will be assigned to the intervention condition. The primary outcomes are changes in stigma resistance and self-stigma from baseline to 4-week follow-up using self-report. We will assess implementation and process outcomes to inform future intervention refinement.

Primary Outcome Variables

This social-behavioral intervention is theorized to change attitudes and beliefs in the short term. The primary attitudinal outcomes indicating **preliminary effectiveness** are stigma resistance and self-stigma. Improvements in stigma resistance are expected to give participants the cognitive and behavioral tools to challenge internalized stigma and resist

fearing enacted stigma,[9,10] which will in turn improve secondary psychosocial outcomes for participants, such as self-esteem and hope.[11–15]

Feasibility outcomes include implementation feasibility and user feasibility. Implementation feasibility outcomes include recruitment rate (% screened who are deemed eligible, % screened who proceed to consent and enrollment), retention rate (% enrolled who complete post-survey), time from recruitment initiation to sample saturation, and intervention engagement (message response rate and mean response time). User feasibility outcomes include phone access, phone plan challenges, and technological literacy during the intervention.

Acceptability outcomes include the seven component constructs of the Theoretical Framework of Acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy.

As this is a feasibility trial, long-term behavioral outcomes will not be measured. However, we expect that reductions in self-stigma from the intervention may attenuate the 'why try?' effect and have distal effects on behavioral outcomes like treatment- and harm reduction-seeking which, in turn, may reduce the risk of drug overdose.[16–19] These outcomes could be assessed in future clinical trials if the pilot demonstrates feasibility, acceptability, and preliminary effectiveness.

Number of Participants

The proposed sample size is 30. As the primary goal is to assess feasibility and acceptability, not effectiveness, sample size is not based on anticipated effect sizes. Previous guidance has indicated our proposed sample size is an acceptable number for feasibility studies.[20–22] This sample size will allow us to estimate the retention rate to within a 95% confidence interval of +/- 12% (calculated assuming a retention rate of 85%). Although exploratory only, the sample size will further allow us to detect moderate effect sizes in the continuous outcomes (Cohen's d = 0.53) with 80% power (alpha = .05, two-tailed) using paired t-tests.

Based on our prior work recruiting from the same population using identical eligibility criteria, we estimate that 40 prospective participants will need to be screened to achieve our sample size.

Visit Schedule

Baseline visit: All participants. In-person. Computer-assisted self-interview (CASI) survey, program orientation, enrollment.

4-week follow-up visit: All participants. In-person. CASI survey.

Telephone interview: Sub-sample of up to 12 participants. Via telephone. Completed within 2 weeks of follow-up visit.

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1. Statement of Compliance

This study will be conducted as specified in the protocol and in accordance with the *International Conference on Harmonisation Guidelines for Good Clinical Practice* (ICH E6), the *Code of Federal Regulations on the Protection of Human Subjects* (45 CFR Part 46), and other applicable requirements (e.g., National Institutes of Health, National Institute on Drug Abuse).

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the *Institutional Review Board* (IRB) for review and approval. Approval of both the protocol and consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. In addition, all changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

If required by the IRB, the master protocol document, informed consent form, recruitment materials, and all participant materials will be submitted to the *Scientific Review Committee* (SRC) prior to IRB review (research.unc.edu/clinical-trials/src).

All personnel involved in the conduct of this study have completed human subjects protection training.

Name of Investigator of Record: Adams Sibley

Signature of Investigator of Record: Adams Sibley

Date: 12.08.2023

2. Background

Substance use disorder (SUD) stigma is an important barrier to ending the opioid epidemic, yet research on this phenomenon is deficient. Nearly 850,000 Americans have died from overdose in the past two decades, and mortality reached an all-time high during the COVID-19 pandemic. SUDs are more highly stigmatized than other health conditions (e.g., HIV, mental illness). SUD stigma prevents uptake of treatment and harm reduction among people who use drugs (PWUD), contributing to needless morbidity (e.g., infectious disease) and mortality (e.g., overdose), and explains in part why only 6.5% of Americans with SUD received past year treatment. Though key federal agencies have identified stigma as a strategic priority in the epidemic, little is known about how to conceptualize and address SUD stigma compared with other health conditions.

Strategies to address SUD self-stigma, in particular, are severely lacking. Self-stigma manifests in PWUD as internalized stereotypes and fear of experienced stigma, leading to the so-called 'why try' phenomenon in which the stigmatized are disempowered from pursuing life goals. SUD self-stigma is associated with numerous psychosocial outcomes including depression, anxiety, diminished quality of life, maladaptive coping and leads to delays in treatment and harm reduction seeking and retention. To date, SUD interventions have overwhelmingly targeted public stigma such as treatment provider attitudes, while there is a remarkable dearth of evidence-based interventions for addressing self-stigma in PWUD. More research is needed to identify strategies that empower PWUD to resist and overcome stigma, especially given the promise of self-stigma interventions in conditions like HIV/AIDS and mental illness.

Stigma resistance, a coping strategy that promotes resilience through empowerment and positive identity formation, is a promising approach to reducing self-stigma. Stigma resistance is associated with multiple psychosocial outcomes, including reductions in self-stigma and improvements in quality of life, self-efficacy, hope, help-seeking, and recovery. Stigma resistance includes both cognitive and behavioral strategies, such as catching and challenging stigmatizing thoughts, forming positive alternative identities, and empowering oneself through learning about substance use. These strategies align directly with techniques used in the HIV/AIDS and mental illness self-stigma intervention literature. Stigma resistance thus serves as an ideal conceptual framework and menu of strategies for self-stigma reduction interventions for PWUD.

The proposed trial builds on the success of the Ohio Opioid Study (OHOP), a rural opioid intervention study (Miller, W.C., Go, V.F., mPIs; UNC IRB #s 20-0660, 17-1887). Qualitative and quantitative findings from OHOP indicated that there is a high level of self-stigma among PWUD residing in southern Ohio. These findings have been corroborated in the PI's dissertation research to date (aims 1 and 2, approved under the above IRB #s), in which PWUD elaborated on their experiences with stigma and provided feedback on the proposed intervention. Participants in qualitative aim 2 (n=22) expressed strong need and enthusiasm for the intervention.

Text messaging is a scalable and cost-effective modality for health behavior change with demonstrated acceptability and effectiveness in interventions with PWUD, a historically hard-to-reach group. Building on our six years of research experience with PWUD in southern Ohio, we will pilot and evaluate a stigma resistance automated text message intervention for PWUD.

3. Rationale/Significance

3.1 Problem Statement

The United States is experiencing a drug overdose epidemic that shows no signs of abating. In the past two decades, 841,000 Americans have died from overdose, of which over 500,000 involved opioids.[23,24] Urgency to address the epidemic reached new heights during the COVID-19 pandemic;[25] an estimated 93,398 people died from overdose in 2020, a record number that eclipsed the previous 12-month total by nearly 30%.[23] Appalachia, where our study is situated, continues to be disproportionately burdened by the opioid epidemic.[26–31]

Substance use disorder (SUD) self-stigma is a barrier to treatment and harm reduction utilization. Among highly stigmatized health conditions, SUD stigma is particularly striking: the general public sees PWUD as significantly more blameworthy and dangerous than people with mental illness, and drug-related stigma is higher than HIV stigma among individuals with both conditions.[32–34] SUD stigma is associated not only with increased drug use and overdose,[35–37] but with many indicators of healthy functioning and recovery, including depression, social isolation, suboptimal healthcare, social and familial rejection, and employment discrimination.[38–42] Self-stigma (self-devaluation and fear of enacted stigma) mediates the relationship between perceived public stigma and poor health outcomes[10,12–16]: Feelings of unworthiness and fear of discrimination create what Corrigan et al. call the 'why try' effect, a sense of futility that diminishes health-promoting behaviors among stigmatized individuals.[43] Self-stigma has been reported in multiple studies as a primary barrier to treatment or harm reduction seeking among PWUD, both in rural settings and more broadly,[17,26,27,44–51] and explains in part why only 6.5% of Americans with a SUD received treatment in the past year.[52]

Strategies for addressing self-stigma in PWUD remain poorly understood, especially for PWUD in active use. Intervention researchers have largely ignored the opportunity to address self-stigma, despite recent calls for its inclusion on the SUD stigma agenda.[53] A 2011 meta-analysis of SUD stigma interventions found only one program that addressed self-stigma, with the majority focusing on public stigma (i.e., attitudes and actions of the general public). More recent systematic reviews have likewise been dominated by studies targeting treatment providers, medical students, and other potential stigmatizers.[54–56] Among the few interventions we have identified intervening directly with PWUD, all studies targeted individuals already in treatment or recovery.[10] Research is thus critically needed to develop and evaluate stigma reduction strategies for the 90% of Americans with SUDs not receiving treatment.[52] By piloting a SUD stigma intervention with PWUD in active use, our study will characterize the feasibility, acceptability, and preliminary effectiveness of one such strategy that may buffer the effects of stigma on poor health among PWUD. Our study will offer lessons in implementation that will inform future intervention efforts in this population.

Effective health communication modalities are needed to promote behavior change in PWUD. PWUD have been defined as hard-to-reach, and substance use researchers face challenges in recruitment and retention.[2] Text messaging is one method that has been successfully used with PWUD and other hard-to-reach populations.[3,4] In addition to its cost effectiveness, text messaging is an effective vehicle for behavior change across multiple health domains,[5] including substance use and mental health,[57–61] and PWUD have deemed text messaging an acceptable way to receive health messaging and share sensitive information across multiple

intervention studies.[6–8] Text message interventions with PWUD have demonstrated significant reductions in drug use, HIV risk behaviors, depression, and anxiety, and increases in recovery self-efficacy and medication adherence.[62–67] In one trial, automated text messages actually outperformed peer supporter-delivered messages in reducing drug use and risk behaviors, indicating that the automated modality may in some cases be as effective as traditional therapeutic approaches.[67] Our study will contribute to the growing literature on the acceptability and effectiveness of text message-based interventions for people who use drugs within the novel context of stigma reduction. Stigma reduction mHealth interventions have recently been piloted with people living with HIV and people at risk for suicide, lending promise to such an approach with PWUD.[68–70]

Identifying low-burden, accessible, and scalable interventions is critical for reaching the majority of PWUD. Ultimately, our findings will add to the critically underdeveloped toolkit of SUD stigma reduction strategies — a toolkit that is essential to ending the overdose epidemic.

3.2 Purpose of Study/Potential Impact

Across three systematic reviews of substance use stigma interventions published since 2011, only three self-stigma interventions have been documented, including just one in the 21st century.[54–56] We have since undertaken an updated systematic review focused on self-stigma interventions (manuscript in preparation) and identified 11 additional trials with evaluation data.[71–81] Although these studies demonstrated some promising evidence of effectiveness (nine had significant improvements in at least one primary outcome), we note three prevailing gaps in the literature that require attention:

1. *Lack of empowerment approaches*: Across 11 studies, 10 included psychoeducational and/or psychotherapeutic components (the 11th provided structural support services like care navigation). No study included an empowerment component. Corrigan and colleagues have called for a greater balance of interventions to restore self-esteem and promote empowerment among PWUD, noting that the 'self-worth agenda' is a necessary complement to public stigma reduction efforts in the overdose epidemic,[82–84] while researchers have also called for more strength-based approaches to addressing stigma.[85]

2. *Lack of programs for PWUD in active use*: Participants in eight of the studies were enrolled in inpatient or intensive outpatient treatment programs for substance use; only three recruited PWUD in active use. Given 6.5% of Americans with SUD received treatment in the past year, strategies are needed to serve the majority of PWUD not currently engaged in care.[52]

3. *Lack of self-help approaches*: PWUD have been described as a hard-to-reach population, with documented challenges in recruitment, engagement, and retention in interventions.[2] All 11 interventions involved face-to-face contact, and eight included a group component. However, structural (e.g., transportation) and intrapersonal (e.g., fear of disclosure) barriers may preclude many PWUD with self-stigma from participating in such programs.[86] Self-help interventions, which allow participants to absorb knowledge at their own pace through websites, apps, or print materials, have demonstrated effectiveness for mental health self-stigma.[86] One such recent pilot used automated text messaging to improve mental wellness using anti-stigma messages and simulated peer

support.[87] Such an approach may be appropriate for PWUD, who have deemed text messaging an acceptable modality for receiving health messaging and for participating in research studies.[3,4,6–8]

To address these gaps, and to build the evidence base of substance use self-stigma reduction strategies, we propose to pilot and evaluate feasibility and acceptability of a novel text message-based intervention with PWUD living in rural Appalachian Ohio.

3.3 Potential Risks and Benefits

3.3.1 Potential Risks

Emotional distress. A small risk of psychological distress (e.g., embarrassment, upset) is posed by study questions concerning stigma. Participants may find answering questions about these issues upsetting; participants will be reminded at the beginning of the pre- and post-surveys that they may decline to answer any questions at any time without any repercussions. Survey administrators will be trained to recognize the signs of distress and how to respond appropriately, including expressing empathy and offering to pause or end the survey with no repercussions to the participant. In our experience using similar data collection methods in the past with people who use drugs, the likelihood and seriousness of this risk is minimal, and we will strive to create a safe and comfortable environment for all study participants.

A secondary source of psychological risk is during administration of the intervention. Though the text message content is positive and affirming, mention of stigma may distress some participants. During the intervention orientation, participants will be provided a list of external counseling and support resources they can access if they feel distressed. These resources will also be shared in a text message during the intervention, along with a text message that the messaging exchange will not be monitored and participants should reach out to the suggested resources if they feel distressed.

Consequences of breach of confidentiality. There is always the possibility of a breach of confidentiality when conducting research. A primary ethical concern of this study is that participation may reveal that participants are engaging in stigmatized behaviors like illicit drug use. Inadvertent disclosure of such information collected during the interviews may subject persons to discrimination and potential social harm. To help minimize the risk of these disclosures, staff will take necessary precautions to keep participant information and participation private. Participant names will not be stored with the survey data. Files - audio, paper, and electronic - will not have any identifying information, and study participants will be tracked through a unique participant study ID#. Interview transcription will be completed in-house by trained study staff. All research data will be stored on a secure, password-protected server at UNC-Chapel Hill, to which only study staff will have access. No participants will be identified in any report or publication that comes from the study.

We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. First, we have a Certificate of Confidentiality from the NIH. Second, all research staff members are required to complete ethical clearance certification regarding protection of human's subjects through UNC-Chapel Hill. Third, the study will safeguard against the risk of the linking information being stolen by keeping such information in a locked Excel file stored on a secure server at UNC to which only essential study

personnel who have completed CITI certification for human subjects' research ethics training (http://citiprogram.org) will have access.

A secondary risk to confidentiality is that the automated text messages, if viewed by an unintended recipient, may suggest that the participant engages in illicit drug use. There are two scenarios where a breach of confidentiality may occur. The first scenario is during the delivery of messages, e.g., they could be intercepted by a third party. However, messages are delivered using Twilio, a service that uses end-to-end encryption and follows industry-standard security measures, certified under ISO/IEC 27001 with additional attestations to ISO/IEC 27017 and ISO/IEC 27018. The risk of breach of confidentiality in this scenario is extremely low. The second scenario is during receipt of the messages. For example, a person other than the participant may read the messages and deduce that they use illicit drugs. To protect against this risk, during orientation, participants will be trained to secure their phones (i.e., password-protecting or fingerprint-protecting) and instructed not to share their phone with anyone for whom unintentional disclosure is a concern. In our formative qualitative research, participants expressed no concerns about inadvertent disclosure in the intervention, so the risk in this second scenario is likely low.

Steps taken to ensure that potential participants do not feel coerced to enter or remain in the study. Research staff recruiting participants will follow a standardized script to ensure that all ethical issues are adhered to and that study protocols are followed. Research staff reviewing consent with all participants will be trained to probe for comprehension. All written and oral communications about the study will emphasize that this study is completely voluntary and will not impact status or position in any organization or setting (including entitlement to services at the harm reduction program serving as our recruitment setting), and that they can drop out of the research at any time without jeopardizing their status or position. Participants will further be reminded that declining to participate or dropping out early will have no bearing on their ability to participate in future research studies at UNC-Chapel Hill or other institutions.

3.3.2 Potential Benefits

Benefits to society. The main benefit of the proposed study to society is the development of a potentially feasible and acceptable text messaging intervention for people who use drugs. The knowledge gained from the study has the potential to fill a critical research gap on acceptable self-stigma reduction techniques and messages in this population. While stigma is acknowledged by experts as a critical barrier to treatment access and utilization, and ultimately a key to ending the opioid epidemic, there are few evidence-based stigma reduction interventions for people who use drugs, and to our knowledge, no self-help interventions that have undergone rigorous evaluation. Our study will further inform whether text messaging is a feasible and acceptable modality for promoting preventive health behaviors in this population. Findings may inform local, state, and national efforts to reduce stigma and encourage service engagement among people who use drugs.

Benefits to participants. The purpose of this study is to determine the feasibility and acceptability of the intervention. However, the intervention is designed to improve psychosocial health outcomes, including reducing self-stigma and improving stigma resistance. The intervention's messages, which are based in evidence-based psychotherapeutic and psychoeducational principles, may improve participant's knowledge about stigma, beliefs about overcoming stigma,

and stigma-related coping skills. The intervention is novel, so it is unclear how likely these benefits are; however, automated therapeutic text messaging interventions have been shown to improve mental health outcomes in the short term. Further, participants in the formative qualitative aim of this study (n=22) expressed strong enthusiasm for the intervention and its content, citing a dire lack of social-emotional support for people who use drugs.

4. Study Objectives

4.1 Hypothesis

As a feasibility study, there is no formal hypothesis testing. Outcomes related to feasibility, acceptability, and preliminary effectiveness will be presented descriptively.

4.2 Primary Objective

We will use an iterative convergent mixed method design[1] to develop and evaluate a stigma resistance text message intervention for PWUD. Text messaging is a scalable and cost-effective modality for health behavior change with demonstrated acceptability and effectiveness in interventions with PWUD, a historically hard-to-reach group.[2–8] Specifically, we aim to:

Aim 1*: Identify PWUD self-stigma subgroups and describe associated demographic, health, and drug use risk factors among rural PWUD in an eight-state multi-site cohort using latent class analysis.*^

Aim 2*: Identify a) stigma-related attitudes and beliefs that are salient to PWUD and amenable to change, and b) text message content and delivery preferences through iterative elicitation interviews with 20 rural Ohio PWUD.*^

Aim 3*: Tailored around findings from Aim 1 and Aim 2, develop an automated daily short message service (SMS) stigma resistance intervention.*^

Aim 4: Evaluate feasibility, acceptability, and preliminary effectiveness of the SMS intervention to increase stigma resistance and reduce self-stigma. We will conduct a pilot trial of the intervention among 30 rural Ohio PWUD in active use and collect quantitative and qualitative data at baseline and four-week follow-up.

Despite wide acknowledgement that stigma is a key barrier to harm reduction and treatment utilization, few studies have intervened on this construct among PWUD in active use. Results of our study will address the current research gap of stigma reduction interventions for PWUD. Our study will further inform whether text messaging is a feasible and acceptable modality for promoting preventive health behaviors in this population.

^ *This study protocol covers Aim 4 only. Aims 1-3 were approved and conducted under separate protocols (UNC IRB# 17-1887 & 18-2747)*.

5. Study Design

5.1 General Design Description

This Phase 1 study is a single-group feasibility trial of a text message intervention to increase stigma resistance and reduce self-stigma among people who use drugs. All participants will be assigned to the intervention condition. The primary outcomes are changes in stigma resistance and self-stigma from baseline to 4-week follow-up using self-report. We will assess implementation and process outcomes to inform future intervention refinement.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

This social-behavioral intervention is theorized to change attitudes and beliefs in the short term. The primary attitudinal outcomes indicating **preliminary effectiveness** are stigma resistance and self-stigma. Improvements in stigma resistance are expected to give participants the cognitive and behavioral tools to challenge internalized stigma and resist fearing enacted stigma.[9,10] Stigma resistance will be measured using the Stigma Resistance Scale.[88] Self-stigma will be measured using the Substance Abuse Self-Stigma Scale.[10]

Feasibility outcomes include implementation feasibility and user feasibility. Implementation feasibility outcomes include recruitment rate (% screened who are deemed eligible, % screened who proceed to consent and enrollment), retention rate (% enrolled who complete post-survey), time from recruitment initiation to sample saturation, and intervention engagement (message response rate and mean response time). User feasibility outcomes include phone access, phone plan challenges, and technological literacy during the intervention.

Acceptability outcomes include the seven component constructs of the Theoretical Framework of Acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy.

As this is a feasibility trial, long-term behavioral outcomes will not be measured. However, we expect that reductions in self-stigma from the intervention may attenuate the 'why try?' effect and have distal effects on behavioral outcomes like treatment- and harm reduction-seeking which, in turn, may reduce the risk of drug overdose.[17–19,33] These outcomes could be assessed in future clinical trials if the pilot demonstrates feasibility, acceptability, and preliminary effectiveness.

5.2.2 Secondary and Exploratory Outcome Variables

The intervention is theorized to affect the following secondary psychosocial outcomes for participants: self-esteem and hope.[11–15] Self-esteem is measured with the Rosenberg Self-Esteem Scale.[89] Hope is measured with the Adult Dispositional Hope Scale.[90]

We will also explore the following categorical demographic characteristics in subgroup analyses of the effectiveness outcomes: age, race, gender, educational attainment, drug of choice.

6. Study Population

6.1 Study Population

Study participants are people who use drugs (PWUD), an appropriate population for receiving stigma reduction interventions. PWUD are disposed to high levels of substance use stigma, which, compared with other health stigmas, is particularly strong (Luoma, 2011).[49] For instance, the general public considers PWUD to be significantly more dangerous and blameworthy than people with mental illness, and substance use-related stigma is higher than HIV-related stigma in people with both conditions.[32–34,91]

Participants will be recruited from Scioto County, Ohio, a rural county designated distressed by the Appalachian Regional Commission with regard to economic status.[92] Southern Ohio has long been a hotspot in the opioid epidemic, with overdose and infectious disease rates outpacing the rest of the state and nation since the turn of the century.[93,94] Portsmouth, the county seat of Scioto and largest town in the region, has often been portrayed in the media as an archetype of the epidemic and was featured prominently in the book *Dreamland: The True Tale of America's Opiate Epidemic*.[95–97] Portsmouth also has a strong treatment and harm reduction infrastructure, with multiple inpatient and outpatient clinics, an established syringe service program (SSP), and at least 37 providers waivered to prescribe buprenorphine.[98,99] Given the study team's research experience and established relationships in the region, along with the salience of stigma described by PWUD in formative aims of this study, Scioto County serves as an ideal recruitment site for this study.

6.1.1 Number of Participants

The proposed sample size is 30. As the primary goal is to assess feasibility and acceptability, not effectiveness, sample size is not based on anticipated effect sizes. Previous guidance has indicated our proposed sample size is an acceptable number for feasibility studies.[20–22] This sample size will allow us to estimate the retention rate to within a 95% confidence interval of +/- 12% (calculated assuming a retention rate of 85%). Although exploratory only, the sample size will further allow us to detect moderate effect sizes in the continuous outcomes (Cohen's d = 0.53) with 80% power (alpha = .05, two-tailed) using paired t-tests.

Based on our prior work recruiting from the same population using identical eligibility criteria, we estimate that 40 prospective participants will need to be screened to achieve our sample size.

6.1.2 Eligibility Criteria/Vulnerable Populations

Inclusion criteria:

1. Ages 18 and older at enrollment
2. Residing in Scioto County, Ohio at time of enrollment
3. Able to speak and read English
4. Reliable daily access to smartphone with a data plan capable of sending and receiving SMS text messages during the intervention period (4 weeks)
5. Self-reported past 30-day use of illicit opioids (e.g., heroin, fentanyl), prescription opioids not as prescribed (e.g., oxycodone, buprenorphine), methamphetamine, or cocaine.
6. Willing to provide informed consent

Exclusion criteria:

1. Unable to be consented due to cognitive impairment
2. Planning to move out of the study area during the study period
3. Unwilling or unable to comply with protocol requirements
4. Currently incarcerated in a correctional facility

No participants will be excluded on the basis of race, gender, or ethnicity.

7. Methods

7.1 Intervention

7.1.1 Description of Intervention

Project RESTART (**Re**sisting **ST**igma **A**nd **R**evaluating your **T**houghts) is a theory-informed, 4-week automated text message intervention to address self-stigma in people who use drugs. The intervention delivers two daily messages to participants for four weeks (56 messages total). Messages are designed to address the four components of the personal level of Stigma Resistance Theory: Not believing stigma/catching and challenging stigmatizing thoughts; empowering oneself through learning about substance use and one's own recovery; maintaining one's recovery and proving stigma wrong; and developing a meaningful identity and purpose apart from one's substance use. The preliminary library of messages was developed by the study team, who have expertise in stigma (Go, Sibley), substance use (Go, Miller, Sibley), health communications (Noar, Sibley), and mHealth (Gottfredson-O'Shea, Muessig, Noar). To ensure all messages are informed by communication and behavioral health theory and accurately map onto the stigma resistance domains, the team created a message development matrix, which was adapted from steps 1 and 2 of Intervention Mapping, an evidence-based protocol for designing interventions. Messages were then pilot tested (IRB #17-1887) with people who use drugs and revised based on their feedback. Message content is informed by evidence-based psychotherapeutic approaches (e.g., Acceptance and Commitment Therapy) and health communication theory (e.g., Elaboration Likelihood Model).

At the baseline visit, participants complete a Computer-Assisted Self-Interview (CASI) survey, are oriented to Project RESTART, and are enrolled to receive text messages to their personal cell phone. Participants then receive two daily automated text messages (morning and evening) which provide psychoeducation about substance use and stigma, advice for coping with stigma, and suggestions for how to set personal goals and build self-esteem. After the 4-week intervention period ends, participants return for their follow-up visit where they will complete a follow-up CASI survey. A subset of participants (n=12) will complete a follow-up telephone interview to provide detailed feedback on the acceptability of the program.

7.1.2 Method of Assignment/Randomization

This is a single-group, pre-post design. All participants will be allocated to the intervention group and receive the same library of automated text messages.

7.1.3 Selection of Instruments/Outcome Measures

Preliminary Effectiveness Outcome Measures

Preliminary effectiveness outcome measures were selected based on construct validity to the outcomes and internal consistency reliability.

Construct	Measure	Example Question

Stigma resistance	Stigma Resistance Scale (Firmin, Lysaker, et al., 2017) 20 items, Likert-type, α=.93	"I challenge negative thoughts that I may have about myself related to my substance use."
Self-stigma	Substance Abuse Self-Stigma Scale (Luoma et al., 2013) 40 items, Likert-type, α=.86	"I feel inferior to people who have never had a problem with substances."
Hope	Adult Dispositional Hope Scale (Snyder et al., 1991) 12 items, Likert-type, α=.77-.84	"Even when others get discouraged, I know I can find a way to solve the problem."
Self-esteem	Rosenberg Self-Esteem Scale (Rosenberg, 1965) 10 items, Likert-type, α=.77	"I feel I do not have much to be proud of."
Covariates	Age, race, gender, educational attainment, drug of choice (all categorical	N/A

Implementation Feasibility Measures

Measures indicating feasibility of implementation include recruitment rate (% screened who are deemed eligible, % screened who proceed to consent and enrollment), retention rate (% enrolled who complete post-survey), time from recruitment initiation to sample saturation, and intervention engagement (message response rate and mean response time).

User Acceptability and Feasibility Measures

User acceptability and feasibility will be measured at post-test only. Items were developed using the Theoretical Framework of Acceptability (TFA). The TFA was developed in light of poor guidance and inconsistent definitions in the literature on assessing acceptability in healthcare interventions (Sekhon et al., 2017). Questions address the TFA's seven component constructs of acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy.[100,101]

User Feasibility and Acceptability Measures

Sub-domain	**Question**	**Response Options**	**Notes**
Feasibility			

User	Before the start of this program, how often did you send or receive text messages?	a. Every day b. A few times a week c. A few times a month d. Less than once a month e. Never	From Lian et al., 2022[102]
	Before the start of this program, how comfortable were you with sending or receiving text messages? Please select the statement that best applies to you.	a. Not comfortable at all b. Not comfortable c. Neutral d. Comfortable e. Very comfortable	From Lian et al., 2022
	Between the start of the program and now, did you experience any challenges or changes with your phone (e.g., lost, broken) that prevented you from receiving or reading text messages?	a. Yes b. No c. Unsure	From Lian et al., 2022
	Between the start of the program and now, did you experience any challenges or changes with your phone number or phone plan (e.g., changed number, ran out of minutes) that prevented you from receiving or reading text messages?	a. Yes b. No c. Unsure	From Lian et al., 2022
	What device did you use to receive text messages for this program?	a. Basic cell phone (non-smartphone) b. Smartphone c. Tablet d. Program on computer or laptop e. Other: (please specify)	From Lian et al., 2022

	On average, when would you read the text message you received?	a. As soon as you saw them b. Later that day c. Later that week d. More than one week later e. Never	From Lian et al., 2022
Acceptability			
Affective Attitude	Overall, how much did you like or dislike the text message program?	a. Strongly dislike b. Dislike c. Like d. Strongly like	From Sekhon et al., 2022
Burden	How much effort did it take to engage with the text message program?	a. No effort at all b. A little effort c. A lot of effort d. Huge effort	From Sekhon et al., 2022
	It was easy to read and understand the text messages.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Lian et al., 2022
	I looked forward to receiving the messages each day.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	
Ethicality	I had concerns about the privacy of my information sent over text message.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Lian et al., 2022
Intervention Coherence	It is clear to me how the text message program can help me to deal with stigma.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Sekhon et al., 2022
Opportunity Costs	Engaging with the text message program interfered with my other priorities.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Sekhon et al., 2022
	How do you feel about the number of	a. Way too few b. Somewhat too few c.	

	messages you received each day during the program (2 messages per day)?	About right d. Somewhat too many e. Way too many	
	How do you feel about the length of the program (4 weeks?)	a. Way too short d. A little too short c. About right d. A little too long e. Way too long	
Perceived Effectiveness	Overall, how helpful did you find the program?	a. Very helpful b. Somewhat helpful c. Barely helpful d. Not at all helpful	From Knutson et al., 2021[103]
	I thought that the topics discussed in the messages were relevant to me.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Lian et al., 2022
	The messages I received were a useful way for me to learn about stigma.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Lian et al., 2022
	The messages I received were a useful way for me to learn to confront stigma.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	From Lian et al., 2022
	The messages I received made me feel better about myself.	a. Strongly agree b. Somewhat agree c. Somewhat disagree d. Strongly disagree	
Self-Efficacy	How confident did you feel about using the information in the text messages?	a. Very unconfident b. Unconfident c. Confident d. Very confident	From Sekhon et al., 2022
General Acceptability	Overall, how acceptable was the text	a. Completely unacceptable b. Unacceptable c.	From Sekhon et al., 2022

	message program to you?	Acceptable d. Completely acceptable	
	How satisfied were you with participating in this study?	a. Very satisfied b. Somewhat satisfied c. Barely satisfied d. Not at all satisfied	From Knutson et al., 2021
	How likely would you be to recommend this program to a friend/family member?	a. Very likely b. Somewhat likely c. Barely likely d. Not at all likely	From Knutson et al., 2021
Message Liking	Please select three messages you liked the most.	[TEXT MESSAGE LIBRARY]	
	Please select three messages you disliked the most.	[TEXT MESSAGE LIBRARY]	
Open-Ended	What did you like about the text message program?		
	What did you dislike bout the text message program?		
	Any other comments about the program?		

Participants will also be asked to rate perceived message effectiveness during the intervention. Once per week (4 surveys total), participants will receive an anonymous Qualtrics link via text message to rate the previous week's messages with the question "Think about the messages you received this week. How effective was each message at changing your feelings about stigma?" rated on a 5-point Likert-type scale from "Not at all effective" to "Extremely effective." No identifying information will be collected in this weekly survey.

7.1.4 Intervention Administration

This automated text message intervention is self-administered, i.e., no interventionists will be engaged in implementation except to recite the orientation script during participants' baseline visit.

Text messages will be delivered via Twilio, a cloud-based communication platform for SMS. Twilio is a secure option for delivering and receiving text messages and has been used in multiple mHealth intervention studies. The messaging program will be developed in Python version 3.11.0, a programming language that is compatible with Twilio's application programming interface. Python scripts, message libraries, phone number database, and other files needed for automation will be stored in AWS Lambda, Amazon's secure serverless computer service for running code. The program will be triggered to run every 15 minutes with Amazon EventBridge Scheduler using cron expressions, ensuring that messages will be sent to participants' phones at their preferred times each day.

7.1.5 Reaction Management

Though the text message content is positive and affirming, mention of stigma may distress some participants. During the intervention orientation, participants will be provided a list of external counseling and support resources they can access if they feel distressed. These resources will also be shared in a text message during the intervention, along with a text message that the messaging exchange will not be monitored and participants should reach out to the suggested resources if they feel distressed.

7.2 Study Procedures

7.2.1 Study Schedule

The study includes 3-4 visits for participants.

1. Screening (pre-enrollment): Participants will be screened for eligibility pre-enrollment at the recruitment site or over the phone. Expected duration is 5 minutes.

2. Baseline Visit (Day 0): Participants will provide informed consent, enroll in the intervention, complete baseline survey, and receive intervention orientation. Expected duration is 1-1.5 hours.

3. Follow-up Visit (Day 28-35): Within 1 week of the end of each participant's 4-week intervention enrollment period, participants will return for their follow-up visit and complete the follow-up survey. Expected duration is 1-1.5 hours.

4. Telephone Follow-up Interview (Day 28-49): Within 2 weeks of the follow-up visits, *selected* participants (n=12) will complete a brief follow-up interview by telephone. Expected duration is 30 minutes.

Total duration of participation will vary depending on participants' availability for follow-up and can range from 28-49 days.

7.2.2 Informed Consent

Written voluntary informed consent will be obtained from each study participant. The consent procedures will be conducted with interested participants before any study activities are carried out.

Participants who are eligible for the study will be approached by a study team member regarding the possibility of participating in the study. They will be reassured that their decision to

participate in the study or not will not affect their relationship with any program or organization, including but not limited to UNC-Chapel Hill and the SHRPS harm reduction program. If the participant is agreeable, the study coordinator will explain the study in-depth in plain language, including the possible risks and benefits to participating in the study. After reviewing the informed consent form, the study team member will reiterate that participation is voluntary and then provide time and opportunity for the participant to review the document again and ask any questions or share any concerns. Once all questions have been answered, potential participants will be told they have the opportunity to provide informed consent, decline to participate, or take additional time to consider participation (e.g. go home and return later). If they agree to participate, the study team member and participant will both sign and date the informed consent form. The participant will be offered a hard copy of the form to take home.

Study staff performing consent procedures will be trained to probe for comprehension to ensure the participant understands the purpose and procedures of the study, their rights as a research participant, the voluntariness of the study, and the risks and benefits of participation.

7.2.3 Screening

Prospective participants expressing interest at the point of recruitment will be offered the opportunity to determine their eligibility to participate in the study via an oral screening process. These prospective participants may choose to a) screen on-the-spot in a private location, b) receive the study phone number to contact the study team for screening over the phone, or c) arrange a later time, date, and location to meet with study team to screen in-person. Study staff will use a standardized screening script to determine participant eligibility.

As recruitment feasibility is a study outcome, all prospective participants will be logged, regardless of enrollment status. Participants who decline to participate or are determined ineligible will be logged with a non-identifying ID code (i.e., based on the date and order of recruitment) and the reason for ineligibility/non-participation. As the screening is oral only, no data will be recorded during the recruitment and screening process, and thus no data will need to be destroyed.

7.2.4 Recruitment, Enrollment and Retention

Recruitment. Participants will be recruited with the help of local organizations, including SHRPS, the area's harm reduction program, and word-of-mouth referral by study participants. SHRPS has served as a partner for recruitment in substance use studies conducted by our co-investigators (Go and Miller) for the past 6 years. Prospective participants will be identified with the help of organization staff. Study staff will also distribute flyers with study contact information during program open hours. With approval of community-based organizations, participants may be recruited by distributing flyers to potential participants. Participants consenting to be re-contacted in the formative portion of the study (IRB #17-1887) may also be re-contacted by phone to inform them of the study.

If participants want to find out more about the study, we will ask the participant to move to a location where others cannot overhear their conversation. In-person discussions with potential participants will occur in private offices. If speaking to a potential participant over the phone, we will ask the individual to move to a location where others cannot overhear the

participant's telephone conversation. Prospective participants expressing interest will be screened for eligibility before scheduling baseline visits.

Enrollment. Individuals will be asked to have their smartphone with them for the enrollment visit. To confirm an individual meets the smartphone eligibility criterion, study staff will confirm that the individual has a smartphone with a data plan at the visit. Individuals will then be screened to confirm eligibility at the start of the enrollment visit.

Individuals meeting eligibility criteria will be guided through an informed consent process by research staff. Individuals will first be able to read or have read to them the informed consent sheet with the opportunity to have any questions answered by the interviewer. Prior to signing the consent document, staff will go through a brief comprehension check with the participant in order to ensure that the participant fully understands all study procedures. Informed consent will cover all procedures, potential risks, benefits and who to contact to report complaints. Study staff will confirm whether consent was obtained and the participant's enrollment status on a study case report form.

After consent is obtained, participants will complete a computer-assisted self-interview (CASI) baseline survey hosted on Qualtrics, a secure HIPAA-compliant platform. Participants will then be given a brief oral orientation to the intervention.

Participants will be considered enrolled upon meeting eligibility criteria, signing the consent form, completing the baseline CASI survey, and successfully enrolling in the text messaging program on their phones.

Retention. We will collect multiple forms of participant contact information and study-related communication preferences (e.g. email, phone/text, social media handles) as part of study enrollment. Using a participant locator form at the baseline visit, participants will indicate which forms of contact they prefer if they cannot be reached on their primary phone. If the participant consents for a friend or family member to be contacted for follow-up, no details of the study will be shared, only that the participant is being contacted about a health study.

Likelihood of recruitment success. There is a high likelihood that we will have access to the anticipated sample size (n=30). Our study team has successfully met recruitment quotas across several quantitative and qualitative research projects in southern Ohio over the past 6 years, including formative qualitative interviews for the current study (n=22), which were completed in 3 weeks in October 2023. The primary recruitment site, SHRPS, is frequently utilized for harm reduction services by people who use drugs. In 2021, SHRPS had 2,199 unique visitors and 12,111 interactions. The program is operated by the Portsmouth Health Department three days a week. The SSP has served as a recruitment site for more than four years in the parent study. SHRPS is well-situated for recruitment given the trust, safety, and legitimacy it has cultivated with the local PWUD community.

7.2.5 Study Visits

Baseline visit (1-1.5 hours)

- Study staff completes informed consent process with participant
- Participant completes CASI baseline survey

- Study staff reviews orientation script with participant
- Participant completes participant locator form
- Participant is enrolled to receive text message intervention

Follow-up visit (1-1.5 hours)

- Participant completes CASI follow-up survey

Telephone interview (30 minutes)

- Select participants (n=12) complete follow-up telephone interview

7.2.6 End of Study and Follow Up

Participation ends with the participant's final study visit (either the in-person follow-up visit or telephone survey, for selected participants). Study staff will complete a study discontinuation/completion case report form for each participant, regardless of disposition. The form will track the off-study date, off-study reason, and reason for discontinuation for those who left the intervention prematurely (e.g., lost to follow-up, left the study area early).

7.2.7 Removal of Subjects

Enrolled participants may withdraw from the study at any time for any reason upon request without penalty. A study discontinuation form will be completed as described in section 7.3.6.

An investigator may withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), serious adverse event (SAE), or other medical condition or situation — related or unrelated to the study — develops after enrollment such that continued participation in the study would not be in the best interest of the participant.
- If a patient presents a safety risk to the research staff.
- If their participation in the study is disruptive to the study.

7.3 Statistical Method

7.3.1 Statistical Design

The pilot trial features a single-group, pre-post quasi-experimental design. As this is a feasibility study, hypothesis testing on the main effectiveness outcomes is strictly exploratory. Analysis assumes a null hypothesis of no participant-level change in the outcome measures from baseline to follow-up. Inferential analysis will be conducted on all outcome measures described in 7.1.3.

Basic descriptive statistics will be calculated for feasibility, acceptability, and outcome measures. We will present frequency tables for the categorical variables and means, standard deviations, and percentiles (25th, 50th, 75th) for the continuous variables. For outcome

measures, descriptive statistics will be calculated for baseline scores, follow-up scores, and change in scores.

Inferential analysis will be conducted on participant-level change in outcome measures from pre to post using paired t-tests (or Wilcoxon signed-ran tests if response distributions are non-normal). We will also examine differences in mean change scores across levels of each demographic variable using ANOVA. Significance levels for analyses will be set at α=0.05. We will use R version 4.3.0 for data cleaning, management, and analysis.

7.3.2 Sample Size Considerations

The proposed sample size is 30. As the primary goal is to assess feasibility and acceptability, not effectiveness, sample size is not based on anticipated effect sizes. Previous guidance has indicated our proposed sample size is an acceptable number for feasibility studies.[20–22] This sample size will allow us to estimate the retention rate to within a 95% confidence interval of +/- 12% (calculated assuming a retention rate of 85%). Although exploratory only, the sample size will further allow us to detect moderate effect sizes in the continuous outcomes (Cohen's d = 0.53) with 80% power (alpha = .05, two-tailed) using paired t-tests. Power calculations were performed using G*Power 3.1.9.7.

7.3.3 Planned Analyses

7.3.3.1 Primary Analyses

The primary outcomes (stigma resistance and self-stigma) and secondary outcomes (hope and self-esteem) will each be measured at baseline and follow-up for all participants. The effectiveness of the intervention will be measured as the mean change in participant-level outcome scores from pre to post given the null hypothesis of no change and a type I error rate of 0.05. We will use an intention-to-treat approach, including all participants with complete pre and post data in analysis regardless of adherence.

Feasibility and acceptability will be characterized descriptively, as described in 7.4.1.

Follow-up telephone interviews will be transcribed and computerized for analysis in the qualitative data analysis program Dedoose (v9.0). Transcripts will be coded and analyzed for emerging themes on intervention acceptability using the Braun & Clarke (2006) approach to reflexive thematic analysis (TA).[104]

7.3.4 Handling of Missing Data

To address missing data, we will review the frequency of missing and non-missing values for all variables at baseline and follow-up. We will conduct missing value analyses to determine whether persons with missing values are systematically different from those without missing values. If this assessment of the frequency of missing data suggests that bias may be introduced, we will employ multiple imputation to address the missing data.

8. Trial Administration

8.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Written voluntary informed consent will be obtained from each study participant. The consent procedures will be conducted with prospective participants before any study activities are carried out.

The informed consent procedure follows the UNC-Chapel Hill required consent template including describing the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent forms will use language that is sufficiently simple for lay persons to comprehend.

Participants who are eligible for the study will be approached by a study team member regarding the possibility of participating in the study. They will be reassured that their decision to participate in the study or not will not affect their relationship with any program or organization, including but not limited to UNC-Chapel Hill and the SHRPS harm reduction program. If the participant is agreeable, the study coordinator will explain the study in-depth in plain language, including the possible risks and benefits to participating in the study. After reviewing the informed consent form, the study team member will reiterate that participation is voluntary and then provide time and opportunity for the participant to review the document again and ask any questions or share any concerns. Once all questions have been answered, prospective participants will be told they have the opportunity to provide informed consent, decline to participate, or take additional time to consider participation (e.g. go home and return later). If they agree to participate, the study team member and participant will both sign and date the informed consent form. The participant will be offered a hard copy of the form to take home.

Study staff performing consent procedures will be trained to probe for comprehension to ensure the participant understands the purpose and procedures of the study, their rights as a research participant, the voluntariness of the study, and the risks and benefits of participation.

8.2 Institutional Review Board (IRB) Review

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the UNC-Chapel Hill Institutional Review Board responsible for the oversight of the study. Annual IRB reporting and review is required for the duration of the study.

8.3 Subject Privacy, Confidentiality & Data Management

We will take the utmost caution to protect the confidentiality of participants' involvement in the study and all participant provided information/data throughout all research procedures and data management and analysis. Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. Every effort will be made to ensure that study participants are protected from the risk of breach of confidentiality using a variety of steps to ensure participant data security across all sources.

The results of the research will be disseminated but no participant names or other identifying information will be used in any dissemination materials (published or otherwise).

8.4 Data Collection

Surveys will be completed by participants via Computer-Assisted Self-Interview (CASI) at the baseline follow-up study visits using Qualtrics. Participants will complete the survey in a private room. A trained study team member will be available to answer questions. Follow-up telephone interviews, conducted with a subsample of participants (n=12), will be completed within two weeks or the participant's follow-up study visit. Study data will be stored in a secure, password-protected database on UNC-Chapel Hill servers. Survey and interview data will be uploaded to the database daily.

Participant-related study information will be identified through a participant ID number (PID), derived from the participant's date of enrollment, on all participant case report forms, audio files, transcripts, and CASI files. Participant names or other personally identifying information will not be used on any study documents and will be redacted from interview transcripts.

8.5 Data Quality Assurance

The quality assurance (QA) plan will include the following components:

- Develop standard operating procedures (SOPs) for important processes of the study, including those involving:
    - The data (including: contacting potential participants, data collection, data entry, data cleaning, data storage and transmission);
        - Systematic plan for data cleaning: Data management staff will be responsible for systematically cleaning the data on a regular basis, at least weekly, to prevent systematic problems with data collection from occurring. Discrepancies in data or missing data found during data cleaning will be investigated by the data manager by meeting with the survey administrator and data management team and referring to source documents, when applicable.
    - Modifications of a procedure that may change during the course of the study (due to reasons such as newly published data, guidelines, or changes in local policies or regulations, etc.). Revisions should be documented with the date of change and approved by the PI; all changes must be documented and communicated to the study staff.
- Ensuring all study staff are trained on relevant SOPs (including the protocol they are carrying out and all data collection forms), before study initiation and annually thereafter with refresher trainings.
- Ensuring all interviewers are extensively trained and will practice conducting study-related interviews, for both qualitative and quantitative data collection.
- Data management staff will produce data error reports on a weekly basis. The Data Manager will review data error reports weekly, and immediately bring any errors identified to the attention of appropriate staff for correction. Errors will be corrected within 3 working days of identification.

- Data entry and transmission reports generated by the electronic data system, if applicable, will be reviewed by the data manager to assure that transmitted data was successfully entered into the database. Errors will be brought to the attention of the responsible person and corrected within 3 working days of identification.
- New data staff members will have all records reviewed by the data manager during their first 1-2 months of employment or until their competency is determined to be at the level of other staff. If necessary, a more intense monitoring regimen is instituted according to the auditing results and needs of the new staff member.

Quality assurance checks will be implemented throughout the data collection process to quickly identify and rectify potential problems. Survey instruments will employ skip patterns and built-in checks to minimize discrepant and unrealistic answers. Standard data cleaning procedures will be used prior to analyses, including outlier detection and graphical representation of the data.

8.6 Access to Source

The study PI and mentor will ensure the availability of all study-related records for audit by NIH, NIDA, and UNC IRB, including participant records, consent forms, case report forms, and supporting source documentation for the purpose of ensuring the protection of study participants, compliance with the protocol and regulatory policies, and accuracy and completeness of records.

8.7 Data or Specimen Storage/Security

All records will be identified by coded number only to maintain participant confidentiality. The data collected from individuals will be stored using a numerical system to identify each subject. Only the staff working on this study (Principal Investigator and Co-Investigators) will have access to the records and identities of the subjects. Any physical study-related information (e.g., informed consent forms) will be stored securely in locked filing cabinets with access limited to authorized study staff. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. Electronic study records, e.g., survey responses, interview transcripts, and case report forms, will be stored on a secure, password-protected university-hosted server (Microsoft OneDrive/SharePoint). Only study staff approved by the UNC IRB will have access to the server.

Qualtrics. Qualtrics will be used for study surveys. The UNC Information Security Office has approved Qualtrics for collection and storage of Private Health Information (PHI) and a Business Associates Agreement (BAA) is in place between UNC-Chapel Hill and Qualtrics. Qualtrics uses Transport Layer Security (TLS) encryption (also known as Hypertext Transfer Protocol Secure (HTTPS)) for all transmitted data. Survey data are protected with passwords and HTTPS referrer checking. The data is hosted by third party data centers that are Statement on Standards for Attestation Engagements (SSAE)-16 Service Organization Control (SOC) II certified. All data at rest are encrypted, and data on deprecated hard drives are destroyed by U.S. Department of Defense methods and delivered to a third-party data destruction service. Qualtrics deploys the general requirements set forth by many Federal Acts including the Federal Information Security Management Act (FISMA) of 2002. They meet or exceed the minimum requirements as outlined in Federal Information Processing Standards (FIPS) Publication 200.

Twilio. Twilio is a third-party vendor that will be used for transmitting intervention text messages to participants. Twilio uses end-to-end encryption and follows industry-standard security measures, certified under ISO/IEC 27001 with additional attestations to ISO/IEC 27017 and ISO/IEC 27018. Twilio uses TLS 1.2 to encrypt data in transit between the customer application and Twilio over public networks. Databases housing customer data are encrypted at rest. Twilio is among the most commonly used softwares for transmission of text messages in mHealth intervention trials.

8.8 Retention of Records

We will permanently delete identifying information from the computer server 4 weeks after data collection ends, including participant contact information logs. Only a completely de-identified copy of the dataset will remain on the server after this point. The de-identified copy of the dataset will be deleted five years after study data are published, as required by most journals.

Interview audio files will be uploaded to the secure server within 24 hours of the interview then deleted from the recording device. The audio will be transcribed to text and stored on the server within one week, after which the audio file will be immediately and permanently deleted from the server.

8.9 Data Safety Monitoring Plan

Reporting of AEs and SAEs. Adverse incidents will be reported to the UNC Institutional Review Board and NIH project officers. Potential incidents may include protocol violations, security incidents, breach of confidentiality, or adverse psychological reactions to the intervention.

In case of any adverse event, site study staff will record the incident in the adverse event tracking log and report the incident in writing via email to the PI and mentor within 24 hours of discovering the adverse event. Any adverse events or protocol violations will also be reported to the UNC IRB and NIH within 5-10 days (depending on severity and needed information collection) with follow-up reporting of any pending information, action, or follow-up.

All SAEs will be reported by the PI to the IRB as soon as possible and reported to NIDA within 24 hours of the event by email. A written follow-up must be received by NIDA within 72 hours of the event. The written follow-up will include the date of the event, what occurred, actions taken by project staff, planned follow-up (if any), whether the event appears to be related to the intervention or participation in the study, and whether the participant will continue in the study.

All AE/SAE will also be included in the annual report to NIDA.

Reporting of IRB Actions to NIDA. IRB actions will be reported by the PI to NIDA within 5 working days.

Reporting of Changes or Amendments to the Protocol. Changes or amendments to the protocol will be reported to NIDA within 5 working days.

Process of AE/SAE Collection. Serious adverse events are based on the FDA definition and defined as those that result in death, are life-threatening, result in hospitalization or prolongation of existing hospitalization, a persistent or significant disability, a congenital abnormality or birth defect. Other injuries or medical events may be considered to be serious adverse events when, in the opinion of a physician, they may jeopardize the participant and may require medical or

surgical intervention to prevent one of the above outcomes. For the purposes of this study, substance abuse or dependency alone in the absence of other adverse impact will not be considered to be an adverse event.

AE/SAE Follow-up Plan. Reports on AEs and SAEs wil be reviewed yearly by the PI, mentor, and co-investigators and included in annual reports to the IRB and NIDA. *See Section 4.2 above for details on AE/SAE reporting.*

Additionally, study staff will remind participants to report any physical or social harm to the study staff immediately, so that participants may receive counseling or other assistance. When necessary, referrals to a psychiatrist or physician will be made.

Responsibility for Data and Safety Monitoring. The PI and mentor are ultimately responsible for data and safety monitoring. The QA processes above ensure that the PI and mentor will be aware of important study-related issues on a weekly basis. The PI will monitor all day-to-day study procedures. If an adverse event occurs, the PI will immediately report the event to the mentor, or in her absence, co-investigator Miller, mPI of the parent grant.

We will establish a safety monitoring committee (SMC) comprising at least three people. The SMC will meet at the outset of the study in person then semi-annually by telephone or in person. The semi-annual SMC meeting will assess whether study objectives are being met and will ensure that benefit exceeds harm. The SMC will review the protocol, assessments, and consent forms prior to study initiation. The SMC will receive all reports of AEs at the same time that the AEs are forwarded to the UNC IRB. Severe AEs will trigger an immediate meeting of the SMC. Additional meetings of the SMC can be scheduled, as needed, to discuss and resolve AE issues. Members of the SMC will include at least one representative of local health departments, one substance use treatment professional, and one representative of the substance use research community. The SMC will submit minutes following every meeting to the UNC IRB.

Staff Training. All study staff will be trained on confidentiality protection through the university's human subjects training modules prior to beginning their role on the study. The importance of protecting participant confidentiality and any confidentiality issues that arise will be discussed in staff meetings. Should such a violation occur, the study staff must report the event to the PI and mentor immediately after being notified. The study staff will provide the participant with social and emotional support. The study team will try to assist the participant in solving any problems related to loss of confidentiality. A staff member that breaks participant's confidentiality will be put on probation and re-trained on maintaining participant confidentiality. If the same staff member violates a participant's confidentiality a second time, their employment on the study staff will be terminated.

All study staff will be required to complete and maintain valid Human Subjects Research and Good Clinical Practice training certificates from CITI or an equivalent training program prior to working on any aspects of the study.

In addition to reporting of any adverse events, yearly DSM review by the SMC will occur and reports will be sent to the PI, mentor, and co-investigators.

8.10 Study Modification

Given the brief duration of the intervention, it is not expected that modifications to the protocol will be made during the study. Any modifications will be reported to the UNC-Chapel Hill IRB and NIDA program officer. Changes will not be implemented until approval is received from both parties.

8.11 Study Discontinuation

In consultation with NIDA and the UNC IRB, the trial may be stopped if unexpected issues arise suggesting that the intervention or research procedures are causing harm to participants.

8.12 Study Completion

The study completion date is the date of the last instance of data collection from a trial participant, i.e., the date of the last follow-up survey or exit interview, whichever comes last. The research team will notify the IRB of study completion within 30 days of this date.

8.13 Conflict of Interest Management Plan

UNC-Chapel Hill researchers are required to complete conflict of interest (COI) trainings and complete COI disclosures as listed personnel on IRB submissions.

8.14 Funding Source

This study is funded by the National Institute on Drug Abuse through a Ruth L. Kirschstein National Research Service Award (grant no.1F31DA058452-01, PI: Sibley).

8.15 Publication Plan

Per NIH policy ("Final Rule"), trial results must be published to ClinicalTrials.gov no later than 12 months from the study completion date. The Final Rule requires that results information consist of tables of information summarizing: 1) participant flow information, 2) demographics and baseline characteristics of the enrolled participants, 3) primary and secondary outcomes, including results of any scientifically appropriate statistical tests, and 4) adverse events. Adverse event information consists of one table that summarizes all serious adverse events experienced by participants enrolled in the clinical trial, and a second table that summarizes other adverse events that exceed a frequency of 5 percent in any arm of the clinical trial. The Final Rule adds a third table for summarizing all-cause mortality, with the number and frequency of deaths due to any cause by arm.

A summative manuscript detailing trial feasibility, acceptability, and preliminary effectiveness outcomes will be written and submitted to the peer-reviewed substance use or mHealth literatures. To standardize reporting, the manuscript will adapt the CONSORT 2010 extension to pilot and feasibility studies[105] following guidelines for adaptation in non-randomized studies described by Lancaster & Thabane (2019).[106] The intervention will be described using the TIDieR checklist and guide.[107] The manuscript will be submitted to a peer-reviewed journal within 12 months of study completion.

Findings will also be disseminated to the public during the principal investigator's dissertation defense, and a report summarizing primary results may be shared with stakeholders in the study community.

No participant names or other identifying information will be used in any dissemination materials (published or otherwise).

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