Leveraging social determinants via artificial intelligence and peer coaching to address racial disparities in primary care among people who use opioids

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Study Team

This project involves Investigators at four institutions, with three multiple Principal Investigators (mPIs), including Drs. Babak Tofighi (Friends Research Institute/Nathan Kline Institute), Crystal Lewis (NYU/NKI), Helen Maria-Lekas (NYU/NKI). Each Principal Investigator will be primarily responsible for oversight of their assigned study components as described in the **mPI Plan**.

Drs. Joshua D. Lee (Co-I), Ryan McCormack (Co-I), and Eric Oermann will support the MPI team in the successful implementation of Aims 1-3 and serve on the DSMB.

A collaborative ***research support team*** will consist of:

- Research Coordinator (FRI/NKI)
- Graduate Research Assistant/Interviewer (FRI)
- Data analyst (NKI)
- x2 Peer Recovery Coaches (NKI)
- Research Assistant (WCM)

Friends Research Institute (FRI)

The FRI Research Coordinator and Graduate Research Assistant/Interviewer will support the mPI team with patient and clinical staff enrollment, data collection, and oversee the day-to-day management of data collection and management, and quality control data analytic checks.

Dr. Tofighi and the study team will lead development of the text messaging intervention and PRC web dashboard to communicate with patient participants. Dr. Tofighi will be responsible for creating project plans, meeting project timelines, troubleshooting, and resolving technical problems that arise in collaboration with Dr. Oermann.

NYU Grossman School of Medicine (NYUGSOM)

Dr. Eric Oermann will provide general guidance and feedback to the study team in the operationalizing of the AI-driven texting software, including natural language processing algorithms.

Drs. Joshua D. Lee (Co-I), Ryan McCormack (Co-I), and Eric Oermann will provide general feedback to the the MPI team in the successful implementation of Aims 1-3 and serve on the DSMB.

Nathan Kline Institute (NKI)

The two NKI-funded Peer Recovery Coaches will oversee daily intervention activities, including organizing schedules, coordinating and monitoring patient load, scheduling recruitment and enrolling patients, and overseeing, undergoing quality control activities (collecting field notes, brief in-depth interview check-ins, quarterly), supporting and coordinating community engagement activities (meeting with supervisors and frontline clinical and social services staff), and contributing to the intervention integrity and fidelity assessment. They will also lead the training of field staff (e.g. ethics and data collection) and lead coordination of study protocol development for the investigative team.

The Data Analyst will support Dr. Williams (Co-I) in performing statistical analysis in Aim 1.

Cornell University

In Aim 3, identifying intervention-related resources and the comprehensive economic evaluation will be led by Dr. Jalali (Sub-contract PI) with guidance from Dr. Murphy (Co-I). Specifically, the Cornell team will ensure that site-specific information is collected to inform the tailored micro-costing questionnaire for the trial; control for potentially confounding factors in multivariable regressions and identify relevant factors for sensitivity analyses; tailor statistical methods to accommodate site heterogeneity; appropriate price weights for resources required to implement and continually manage each strategy; and conduct a comprehensive economic evaluation of the intervention.

Each site and collaborating investigators/study teams will be responsible for all study procedures, including but not limited to: recruitment, consent, data collection, and data storage and shipment. WCG will be the IRB of Record for the study and therefore will submit all protocol documentation for review and approval and will be responsible for reporting any updates and/or events that occur throughout the study procedures. Data will be collected and stored at both sites (NKI and FRI) with FRI periodically sending the data to NKI. Any process measures pertaining to the text messaging tool will be collected and stored at FRI in partnership with the HIPAA compliant texting vendor, QliqSOFT.

Study Synopsis

Black and Latinx people who use opioids (PWUO) bear a disproportionate burden of opioid overdose deaths. The economic burden faced by Black and Latinx PWUO has also risen due to costs associated with excess mortality and utilization of high-cost healthcare services. Compared to White PWUO, Black and Latinx PWUO are less likely to be initiated on buprenorphine in emergency department (ED) settings and establish care in primary care for the treatment of opioid use disorder (OUD). Racial disparities among PWUO in primary care are driven by social determinants of health (SDH; e.g., lack of peer support or health insurance) and may be partially addressed by adopting innovative *mobile health* and *peer coaching* strategies.

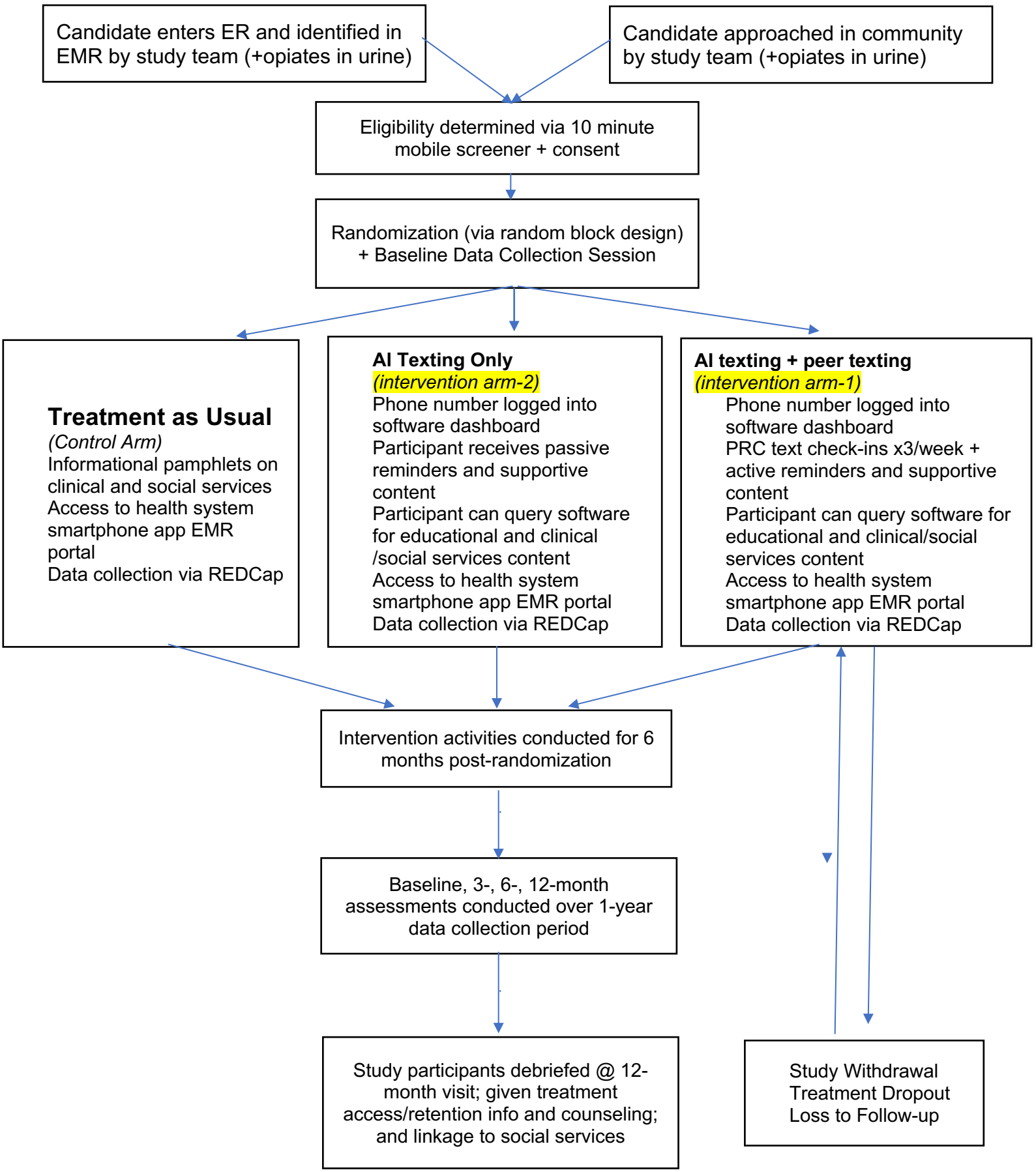
With NIH support, we have validated a theory-driven, *artificial intelligence (AI)-driven texting tool* using natural language processing to facilitate real-time text responses to patient queries combined with automated texts facilitating receipt of buprenorphine in office-based opioid treatment (OBOT) and social services that address social determinants of health (SDH). This open-source texting tool offers *passive* reminders, informational content, *and interactive* two-way response algorithms *without personal staff contact*. In addition, we have adapted an efficacious cultural and structural humility training for PRCs that goes beyond SDH to also address stigma reduction, discrimination, health habitus, and patient navigation to enhance uptake of primary care and social services for PWUO.

Using a three-arm, comparative effectiveness trial design, our specific aims are to: (1) *Assess the efficacy* of PRC supported text-based care/services coordination with PWUO + AI-driven SDH-enhanced text messaging *(intervention arm-1)* vs. AI-driven SDH-enhanced text messaging only *(intervention arm-2)* vs. TAU or printed social/medical services referrals *(control)* to enhance the receipt of buprenorphine in OBOT among community and ED-enrolled Black */* Latinx PWUO (N=252); (2) *Evaluate the implementation of the multimodal intervention (arm-1)* guided by the RE-AIM and CFIR frameworks using in-depth interviews among 3 stakeholder groups: (a) *frontline providers* (n=10); (b) *administrators* (n=10); and (c) a subset of the *Black and Latinx PWUO* from the multimodal intervention arm-1 (n=30); and (3) *Identify the resources and estimate the associated cost* of implementing and sustaining the multimodal intervention and incorporate this information into a customizable budget-impact tool and conduct a comprehensive economic evaluation to calculate the relative economic value (e.g., cost-per quality-adjusted life years, cost-per OUD treatment days) of each study arm from the healthcare sector, state policymaker, and societal perspectives which will also inform implementation framed by RE-AIM.

Study Timeline

Study Activity	Year 1				Year 2				Year 3				Year 4			
	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Survey development	•															
IRB approval	•															
Hiring and staff development	•	•														
Aim 1: Surveys (n=252) - Assess efficacy of PRC-patient text contact + AI-driven text messaging - vs. AI-driven text messaging text messaging only - vs. TAU (i.e., printed social/medical services referrals)			•	•	•	•	•	•	•	•	•	•	•			
Aim 2: In-depth interviews (n=40) - Evaluate implementation of the multimodal intervention						•	•	•	•	•	•	•	•	•	•	
Aim 3: Cost-effectiveness analysis									•	•	•	•	•	•	•	•
Quality Control			•	•	•	•	•	•	•	•	•	•	•	•	•	•
Data Analysis			•	•	•	•	•	•	•	•	•	•	•	•	•	•
Data dissemination: scientific meetings, manuscript development															•	•

Study workflow



Introduction

Aim 1 will proceed in the last 6 months of Year 1. Study start-up, including IRB approval, training of research staff, ClinicalTrails.gov registration, and deployment of our AI texting system will proceed for the first 3 months of Year 1. Enrollment of the first patient-participant will occur at the end of the second quarter and will continue until the first quarter of Year 3. Longitudinal data collection will end in the first quarter of Year 4. Initial analyses for Aim 1 will begin at the end of Year 4. A manuscript reporting the results of Aim 1 is expected in Year 4. Study close-out, including submission of results through ClinicalTrials.gov, is also expected in Year 4.

Aim 2 will begin in the second quarter of Year 2. Participants will be recruited to undergo in-depth interviews (n=50) which will occur until the beginning of Year 4. *Aim 2* analysis will culminate in publications in Year 4.

Aim 3 will begin in the second half of Year 1, with the economics team working alongside the lead team to complete local and sIRB applications. Site visits to identify resources (labor, materials, etc.) required for implementation will also begin in Year 1 and will continue into Year 2. Additional Year 2 activities will consist of the development of a site-level budget impact tool; identification of appropriate price weights for the aforementioned resources; and estimation of implementation costs. In Year 3, the econ team will follow-up with the sites to identify the resources required to sustain the intervention; estimate the associated sustainment costs; conduct an environmental scan; and tailor statistical methods to accommodate site heterogeneity. In Year 4, the economics team will complete the tasks begun in prior years, and ensure that analyses are complete, manuscripts are prepared, and findings are disseminated in a timely manner. A manuscript regarding the required implementation and sustainment costs is expected in Year 4 quarter 1, and the comprehensive cost-effectiveness analysis manuscript is expected at the end of Year 4.

Background

Office-based opioid treatment (OBOT) is effective in reducing opioid overdose[1–4]. However, few primary care physicians prescribe buprenorphine relative to rising overdose deaths, particularly in Latinx and Black American (henceforth Black) communities[5,6]. Treatment drop-out in OBOT remains high among Black (85.1%) and Latinx (84.5%) patients compared to White patients (31.8%) at 1 year[7–9] and is attributed to cultural and social determinants of health (CSDH; e.g., racism, social isolation, food insecurity)[10–12].

Since the COVID-19 pandemic, racial disparities among PWUO has markedly worsened[13]. Opioid overdose deaths among Black / Latinx PWUO are disproportionately higher despite lower rates of opioid use disorder (OUD) compared to White adults[14–19] and are exacerbated by systemic racism[20–26]. During 2020 in NYC, Black / Latinx communities endured high rates of overdose deaths (e.g., Harlem: 56/100,000 persons, Bronx: 49/100,000 persons) compared to their White counterparts (28.7/100,000 persons)[27]. Nationally, racial disparities persist in the provision of OUD treatment services among PWUO in emergency department (ED) settings[28,29].

Integrating telemedicine and mHealth in OBOT offers an evidence-based approach to easing access to buprenorphine[30–34]. Our prior findings during COVID-19 among Black / Latinx PWUO revealed: 1) major reductions in OUD and social services in NYC; 2) preferences among NYC H+H administrators, clinicians, and community pharmacists to expand access to telemedicine-delivered buprenorphine treatment in primary care among ED and community referrals[35–38]; and 3) feasibility of integrating AI-driven texting to facilitate receipt of buprenorphine and naloxone during telemedicine *and* in-person primary care visits[35,39,40].

AI-driven texting offers an innovative approach for remote monitoring of buprenorphine treatment recruitment and engagement with social services. SAMHSA Physician Clinical Support System challenges identified by our team included managing medication dosing and coordinating social services referrals[41]. Further, providers rely on patient-initiated calls to staff to resolve clinical and administrative issues that are rarely used by patients[35,38,42,43]. Texting is *cost-effective* in scaling patient-provider communication and reducing substance use[44–47]. Studies conducted by our team revealed: 1) low rates of acceptability for smartphone applications (30%) versus texting (82%) to reduce illicit opioid use[38,48]; 2) absence of evidence-based smartphone apps supporting PWUO seeking OUD service[49–51]; 3) texting as the most popular mobile phone feature nationally and among underserved Black / Latinx PWUO[38,52–55]; 4) prolific input by Black / Latinx PWUO participants informing the scripting of over 650 texts and delivery preferences (e.g., timing, frequency) to enhance OUD outcomes[56–61]; 5) no prior participant mobile phone privacy issues due to our adoption of federal privacy safeguards; and 6) feasibility of integrating the proposed texting tool to enhance receipt of social services addressing SDH and OBOT entry among community and ED-referrals[62]. The AI-driven texting tool aligns with key objectives outlined in SAMHSA and CDC guidelines to scale sustainable, patient-centered, and risk mitigation strategies that enhance uptake of evidence-based interventions in primary care among Black / Latinx PWUO[33,41,63–68]. The text message content (650+ texts) and delivery frequency is based on extensive mixed-methods studies demonstrating *minimal burden among participants*[56,58,60,61].

SDH-focused cultural and structural humility (CSH) training for peer recovery coaches (PRCs) is uniquely positioned to address racial disparities among PWUO[69,70,71]. Per SAMHSA and consensus guidelines, PRCs with lived experience of OUD[72] are effective in coordinating OUD and social services referrals for peers with these conditions[73–75]. Our CSH training addresses stigmatization of PWUO and can enhance access to primary care by focusing on: 1) the cultural and social determinants of health and health outcomes, including OUD; 2) the health burden of intersectional stigma (e.g., explicit and implicit bias facing racially minoritized PWUO); and 3) strategies for PRCs to establish boundaries while providing support to PWUO that is informed by their own recovery experiences.

Economic evaluations of treatments and services for PWUO provide necessary data to inform decision-making by stakeholders and policymakers. Drs. Jalali and Murphy are leading comprehensive economic evaluations in ongoing NIDA trials assessing the impact of medications (R01DA045042) and services (including mHealth, R01DA048892) on OUD outcomes on PWUO with the clinical team. Similar analyses are proposed here to identify the resources required to implement and sustain the proposed intervention and calculate their economic value for stakeholders. This proposal will leverage the collaborative research experience gained from the completed and in-progress economic evaluations described above, as well as the established mentorship between senior (Dr. Murphy) and early-career (Dr. Jalali) health economists, supported by the CHERISH research infrastructure at Weill Cornell, to ensure the successful completion and scientific integrity of the proposed economic analyses. The economic team has extensive experience evaluating health economic outcomes of treatment interventions for PWUO, including mobile health interventions with the clinical investigators of this proposal[83,108,109,166].

The primary aim of this proposal is thus to determine whether a multimodal intervention that combines artificial intelligence (AI)-driven texting that delivers cultural and social determinants of health (CSDH)-focused content prioritizing access to social services to enhance receipt of OUD services (3-5 texts/daily) in primary care among PWUO combined with peer recovery coach (PRC)-supported text-based care/services coordination that ensures real-time responses for unanticipated social, administrative, and clinical issues to enhance receipt of social services and OUD services (3-4 texts/weekly) can improve receipt of buprenorphine in primary care. j

Study Strategy

The proposed three-arm comparative effectiveness trial will evaluate the *efficacy* of a multimodal intervention among community and ED-enrolled Black / Latinx PWUO that combines: 1) *Artificial intelligence (AI)-driven texting* that delivers cultural and social determinants of health (CSDH)-focused content prioritizing access to social services to enhance receipt of buprenorphine (3-5 texts/daily) in primary care among PWUO (intervention arm-2); 2) *Peer recovery coach (PRC)-supported text-based care/services coordination* that ensures real-time responses for unanticipated social, administrative, and clinical issues to enhance receipt of social services and buprenorphine in primary care (3-4 texts/weekly); and 3) employing a novel and evidence-supported *Cultural & Structural Humility (CSH) training for PRCs that attends to the cultural and social determinants (CSDH)* including contending with intersectional stigma and discrimination through empowerment/advocacy, health habitus insights, and patient navigation (intervention arm-1).

Aim 1 will entail 252 Black / Latinx PWUO screened in the hospital ED and randomized to AI-driven CSDH-enhanced texting + PRC-supported text-based care/services coordination (***intervention arm-1***) vs. AI-driven CSDH-enhanced texting only (***intervention arm-2***) vs. TAU (***control***) defined as receipt of printed social/primary care services referrals. Intervention activities will span 26 weeks and data collection will include in-person or virtual REDCap surveys at baseline-, 3-, 6-, and 12-months, and in-depth interviews following survey period to assess fidelity, implementation, and characterization of intervention efficacy.

Primary outcomes: Participants, regardless of study arm, will complete remote and/or in-person follow-up assessments at 3-, 6-, and 12-months. *The primary outcome for this efficacy study* is self-reported linkage to OUD services (i.e., time to initial buprenorphine prescription that is prescribed in OBOT programs or other OUD treatment providers per the Non-study Medical and Other Services form.

Secondary outcomes include durability of treatment effect at 52 weeks (e.g., continuous retention in OBOT with buprenorphine), receipt of social services, and longitudinal engagement with the proposed intervention (up to 26 weeks)

Aim 2 will evaluate the implementation of the multimodal intervention (arm-2) at 3-, 6-, and 12-months using RE-AIM and CFIR linked to a public hospital setting offering OBOT with buprenorphine. In-depth interviews with frontline providers (n=10), administrators (n=10), and a subset of PWUO participants from intervention arm-2 (n=30) will be interviewed to contextualize patient-, provider-, and systems-level factors influencing intervention delivery.

Aim 3 will identify resources and cost estimates required to implement and sustain the multimodal intervention, incorporate these costs into a customizable budget-impact tool (Aim 3a), and conduct a rigorous economic evaluation to calculate the relative economic value of each arm (incremental cost / QALY) from the healthcare, state-policymaker, and societal perspectives (Aim 3b).

Successfully harnessing mHealth tools to address primary care clinical outcomes (Aim 1)

Over the last decade, our team has refined mHealth strategies to address disparities in primary care**.** Our initial findings demonstrated that the adoption of telephone encounters among Bellevue primary care providers during Hurricane Sandy in 2012 were not associated with any increases in missed appointments (p=0.52) or illicit opioid reuse (p=0.66) at 6 months (N=132)[125,126]. In 2020, our team co-founded the city-wide NYC H+H telemedicine program that provides same-day prescribing of buprenorphine and naloxone (N=199)[35,42,106]. These findings demonstrated that the adoption of a multimodal mobile health strategy offers an innovative risk mitigation strategy to minimize the impact of disasters on primary care engagement among PWUO.

Can the multimodal intervention be equitably implemented in clinical care? (Aim 2)

The RE-AIM and CFIR will be used as process and determinants frameworks that will allow us to adapt the intervention in arm 1 as it is unfolding, and guide the evaluation of its effectiveness from the perspective of key stakeholder groups[197–199]. Specifically, we will assess intervention **R**each (among both PWUO and frontline providers); **E**ffectiveness (defined as PWUO linking with primary care-based buprenorphine treatment and social services, and as successful integration of PRCs in care teams); **A**doption (by providers and administrators); **I**mplementation (assessing fidelity of key implementation features and potential intervention adaptations during implementation, and resources and costs on a systems-level per administrator interviews and economic data analyzed in Aim 3); and **M**aintenance (assessing whether the intervention becomes integrated into routine practice, i.e., assessing the institutionalization of primary care-based buprenorphine treatment and social services. We will complement RE-AIM with the CFIR to evaluate multi-level barriers/facilitators associated with intervention reach, effectiveness, adoption, implementation fidelity / adoption, and maintenance. The CFIR[76] specifies five main implementation determinants, including characteristics of the *Innovation* being implemented, the *Outer and Inner Settings* in which an intervention is being implemented, characteristics of *Individuals* involved with implementing, delivering, and/or receiving the innovation, and the implementation *Process*.

How Cost-Effective is the multimodal intervention? (Aim 3)

For Aim 3, the economic team will work closely with the implementation team to identify and collect data on the resources and estimate the associated cost needed to implement and sustain the intervention using study data and semi-structured interviews with study staff. The resulting information will be incorporated into a customizable budget-impact tool, which will allow the economic team to calculate a per participant intervention cost which will be incorporated into a comprehensive economic evaluation to calculate the relative economic value (e.g., cost-per QALY) of each study arm from the healthcare sector, state-policymaker, and societal perspectives at 6- and 12-month time points. The budget impact tool will serve as a publicly available resource *allowing stakeholders to assess the feasibility and sustainability of the interventions* (or similar interventions) *based on their specific needs and expected costs to their specific setting*.

The economic evaluation will be conducted from multiple stakeholder perspectives. The **healthcare-sector perspective** includes all formal medical costs incurred by the health system on behalf of study participants, including the cost of the intervention and patient out-of-pocket costs. Since Black / Latinx PWUO are at an increased risk of incurring high healthcare costs[85,86], evaluating the extent to which increases in treatment-related services may lead to downstream cost-offsets via decreases in acute care services is critical for decision-making. The **state-policymaker perspective** will be included to inform resource allocation decisions on behalf of the public that is often responsible for funding healthcare among vulnerable populations (e.g.,

Medicaid)[93,94], the direct costs associated with criminal-legal resources, and social safety-net programs (e.g., disability/SSI/unemployment).[95,96] Further, the **societal perspective** accounts for many of the indirect costs, such as reduced school and labor market outcomes[97,98], and costs incurred by victims of crime will also be considered[99,100].

Study Design

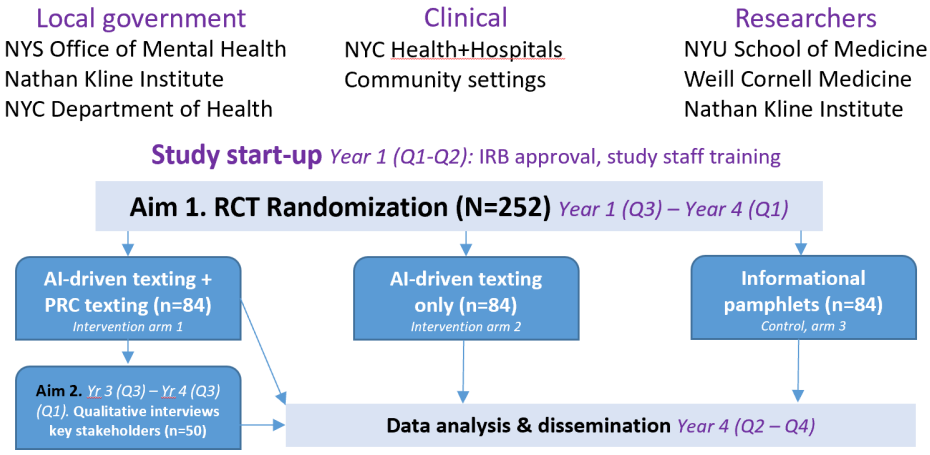
Aim 1: Does AI texting + peer supported texting improve linkage to OUD services?

To achieve Aim 1, potential study participants with opioid use disorder (OUD) will be identified and recruited in the hospital emergency department (ED) and community settings. The study team has over two decades of experience enrolling and tracking patient participants in these high-risk communities. Each of these cohorts includes people who use opioids who are *not prescribed* any medication for opioid use disorder (MOUD), including methadone or buprenorphine, in the 30 days preceding their study enrollment.

Study settings

Planned study sites for participant enrollment will include NYC Health+Hospitals affiliated hospitals (e.g., Lincoln Hospital), the START Treatment and Recovery centers, and community settings associated with high rates of opioid overdose deaths among Black and Latinx adults in New York City.

Figure 1. Aims 1 and 2 Logic Model



The **study sample** of 252 Black and Latinx PWUO with a positive urine toxicology result per the Hospital EMR will be identified by the study team and approached in the ED or in community settings among PWUO self-reporting OUD and confirmed with random saliva toxicology testing and recruited over a 2-year period and followed for a duration of 12-months with purposeful recruitment of male: female adults along a 2:1 target ratio (169 males: 83 females) and a target minimum 25% aged 18-29 (see *Figure 1*). We will use venue-based and street outreach in spaces where opioid-related overdose rates are highest, and in neighborhoods where harm reduction services are located.

Potential study participants will be informed of study details by the study team, undergo informed consent, complete baseline REDCap assessment, and will then be randomized (1:1:1) using a random block design (block sizes 3, 6, 9) to 1 of 3 study arms, stratified by gender. Finally, participants will be compensated for their time at visit end and given an appointment schedule for in-person or remote survey visits. Randomly selected participants from intervention arm 1 (n=30) will be invited for the qualitative implementation interviews (see Aim 2). All randomized participants who need a phone will be provided one by the study and tracked over

time by leveraging Drs. Lewis', Lee's, and Tofighi's study tracking and retention expertise in the event of changes to mobile phone numbers.

Participants will be given instructions to complete remote or in-person follow-up assessments that will be conducted in one of three data collection sites in Manhattan (i.e., NYS OMH Harlem field office site, Lincoln Hospital, and START Treatment and Recovery centers). *All* potential participants will complete informed consent, computer-assisted baseline survey, will be administered the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) for OUD by the study team to differentiate between participants with OUD versus individuals misusing opioids to quell untreated pain symptoms only. Next, participants will be randomized (1:1:1) following a random block design (block sizes 3, 6, 9) to interactive texting + Peer Recovery Coach-supported text contact, interactive texting only, or TAU, and include stratification by gender.

Study posters and flyers will be developed for distribution in the emergency department and community settings.

Participants randomized to **intervention Arm-1** (n=84) will be assigned to receive *AI-driven CSDH-enhanced texting + PRC-supported text-based care/services coordination*. The AI-driven texting goals, operational sequences, and content have been iteratively refined in numerous studies among Black/Latinx PWUO to ensure optimal adoption (see *Table 1*)[129,131]. Text contents are based on federal and consensus guidelines on optimizing medical management for PWUO with buprenorphine[167,168], and addressing CSDH[169–171]. Participants randomized to **intervention Arm-2** will receive the *AI-driven CSDH-enhanced text messaging only* (as described above; see *Table 1*). Participants in this arm (n=84) *will not receive text support from the PRC.* Participants randomized to **control Arm-3** will receive treatment as usual (i.e., verbal instructions, NYC Dept of Health pamphlets detailing access to OUD and social services, health system smartphone application EMR patient portal). No services will be provided except for social/clinical service referrals given at the end of each REDCap visit.

Cohort

The sample size, *N*=252, was chosen to provide sufficient power for analyses associated with the defined primary outcomes and accounting for 20% attrition. In the absence of normative data, based on results of prior studies among emergency department enrolled PWUO that indicate modest uptake of MOUD (~5%[191]), and completing referrals to MOUD services (~25%[192-194]), we compute the power to detect significant effects. Using these estimates as the baseline, we anticipate that interactive texting will increase completing referrals to primary care from 25% to 35%[195-197]. The combination of interactive texting *and* PRC support will enhance time to completing referrals to primary care from 25% to 45%. These anticipated changes indicate odds ratios for intervention versus TAU (effect size) of between 1.5 to 2.0 for OUD-related outcomes. We use these estimated odds ratios (ORs) as the proxy for the rate in treatment versus the control. Evidence from methodological studies assert a useful equivalence involving the hazard ratio (HR), such that when the PH assumption is reasonable, the HR is equivalent to the odds that a randomly chosen person with hazard represented in the numerator will experience the event of interest *before* a randomly chosen person with hazard represented in the denominator[198-200]. The power to detect these effects with α=0.05 (two-tailed) using log-rank comparisons for survival outcomes via the power procedure in SAS v9.4 is ~80%.

Enrollment, Consent and Workflow

Over a 2-year period, Black / Latinx PWUO (N=252) identified in the ED or community by the study team using the electronic medical records (EMR) or self-report will be screened and enrolled by the study team. Specifically, ED-recruited Black and Latinx PWUOs with a positive urine toxicology per the Hospital EMR or self-reporting illicit opioid use among PWUO approached in community settings and confirmed with random saliva toxicology testing will be enrolled over a 2-year period. Community-recruited PWUO participants will complete enrollment in the in private conference rooms located in Lincoln Hospital or START Treatment and Recovery centers or in the NYS OMH Harlem field office site. Given the ethical importance to expand enrollment of vulnerable and hard-to-reach persons living with substance use, including women, unstably housed, and uninsured adults, we will provide reimbursement for peer-driven recruitment ($25, max 3 referrals per participant).

Potential study participants will be informed of study details by the study team, undergo informed consent upon discharge, complete baseline REDCap survey, and will then be randomized (1:1:1) using a random block design (block sizes 3, 6, 9) to 1 of 3 study arms, stratified by gender. Finally, participants will be compensated for their time at visit end and given an appointment schedule for in-person or remote survey visits. Randomly selected participants from intervention arm 1 (n=30) will be invited for the qualitative implementation interviews (see *Aim 2*). **Of note**: All randomized participants who do not have a phone will be provided one by the study and tracked over time by leveraging Drs. Lewis, Lee, and Tofighi's expertise in the event of changes to mobile phone numbers (i.e., participant tracking).

Recruited Black and Latinx PWUO will be followed for a duration of 12-months with purposeful recruitment of male: female adults along a 2:1 target ratio (167 males: 83 females) and a target minimum 25% aged 18-29. Follow-up assessments will be conducted in one of three data collection sites in Manhattan. Alternatively, we will conduct follow-up interview-administered computer-assisted REDCap surveys virtually (video or phone) to mitigate COVID-19 exposure and ensure optimal convenience for study participants. Participants lacking mobile phone ownership will be provided with a phone and subsidized mobile phone payment plan to ensure equal access to participating in the study. The study team will track and record the unique ISBN number for phones purchased in the study. In the event that the study team purchases a surplus of phones that are not offered to patient participants by the end of the study, these phones will be returned to the vendor and a refund receipt will be provided to AHRQ upon request.

PWUO participants will then be encouraged to establish care with OBOT to initiate buprenorphine. These OBOT programs are based on the medical management model by initiating eligible patients on buprenorphine, naloxone, with referrals to specialty care services (e.g., HIV services, psychiatry, hepatology), baseline laboratory testing, and encouragement to engage with self-help groups (AA/NA/DA) and psychosocial counseling.

PWUO participants randomized to intervention arm-1 in Aim 1 will receive AI-driven text messaging combined with PRC supported text message contact. The PRC will complete SDH-focused training through the NKI-CCASE Cultural & Structural Humility Training (CSH)[71]. The integration of PRC into health care systems and service settings is effective in improving engagement with health care and clinical outcomes among persons with OUD[72] and is aligned with the recovery movement, and SAMSHA priorities. Key PRC tasks will consist of: 1) reducing stigma (internalized, anticipated, and experienced) among PWUO; 2) generating cultural and structural humility and self-reflection; 3) enhancing PRC recognition of the cultural and SDH-formed health habitus and behavior; 4) integrating the health habitus of participants into their text

message-mediated coaching; 5) strengthening PRC-participant rapport and communication; 6) bolstering participant navigation skills to ensure optimal engagement with OUD services; and 7) establishing meaningful boundaries between PRC and participants to mitigate role conflict. Trainings will also enhance PRC awareness of social/clinical services, understanding of overdose risk reduction, prevention, and treatment, and addiction training drawn from our earlier work and modified to include the use of primary care-based buprenorphine treatment.

Data Gathered

During the **screening visit**, participants will complete the Screener. At the **baseline visit**, data collection will include Demographics, Locator Form, Urine Drug Screen, Mobile Phone Use Characteristics and DSM V OUD Checklist [228].

Semi-structured surveys will be administered at baseline, 3-, 6-, and 12-weeks among PWUO participants. These surveys include the Patient-Reported Outcomes Measurement Information System (PROMIS)[229] and General Anxiety Disorder 7- item scale (GAD-7)[227]. The Risk Assessment Battery (RAB)[226] will be collected at 6 and 12 months only. **Administrative data** will be collected from the Hospital EHR or self-report to capture PWUO participant utilization of clinical services for exploratory purposes only. **Process measures** logged in the text messaging software will capture PWUO participant engagement with the fully automated AI-driven text messaging tool and PRC-PWUO participant text message contact.

Baseline and follow-up surveys will be identical (with few exceptions i.e., age, sex, race / ethnicity) including: ***Demographic and CSDH characteristics***[172]; and ***PhenX consensus measures***, including the Addiction Severity Index[174],fatal and non-fatal overdose episodes[177,178], intersectional opioid-related stigma[180], Everyday Discrimination Scale,[181] social network characteristics[182] and Medical Outcomes Study Social Support Survey[183], harm reduction and social services use[184], MOUD and Buprenorphine Treatment and Adherence, and Non-Study Medical and Other Services (NMOS) (See *Table 2*).

During follow-up, the ***REDCap Survey*** will capture Timeline Follow Back interview[173] and the domains of the Technology Acceptance Model[187] (see *Figure 2)*: ***perceived usefulness, perceived ease of use***, ***attitudes***, ***behavioral intentions***, *and* ***intervention usage***. In addition, data for each of these components will be derived from: the texting software (e.g., rate of participant responses to software-initiated text queries, number of participant-initiated requests for physician telephone assistance[53,129,188,189]), and through ***PRC communication logs*** and ***qualitative interviews*** to inform fidelity, implementation, and contextualize intervention efficacy, enhancing RE-AIM and CFIR frameworks.

Table 2. REDCap Survey Data Definitions		
Quantitative Domains and Variables		
Baseline & Follow-up *(3, 6, 12 months)*	**Sociocultural & demographic determinants of health**	• Demographic characteristics (e.g., age, gender, race/ethnicity) • Socioeconomic conditions related to education, employment/financial status, family/social relationships, criminal justice involvement (Criminal and Legal Activities Form), family/social relationships, and housing status (Housing Instability Scale) • Structural determinants of health (Social Vulnerability Index) • Individual social determinants of health (Disparate Health Care Quality) • Access to health services (modified National Health Interview Survey) • Access to technology / use for health needs (Health Information National Trends Survey) • Intersectional stigma/discrimination of OUD and other social statuses e.g., race, ethnicity, gender, sexual identity, etc. (Brief Opioid Stigma Scale; Everyday Discrimination Scale)[1] • Social network composition, size, social supports based on instrumental, informational, emotional support domains (Medical Outcomes Study Social Support Survey)
	Substance use & Sexual risk behavior *(outcomes, exposures & confounders)*	• Substance use risk, including type, frequency, route, duration, and locations of illicit substance use (Addiction Severity Index) • Increase, decrease, and persistent use during follow-up (Timeline Follow-Back) • Syringe sharing, polysubstance use, non-fatal overdose (Risk Behavior Survey) • Medical, behavioral health, harm reduction, and substance use treatment utilization (Timeline Follow-Back, Non-Medical and Other Resources) • Cognitive Function–Abilities, Depression, Pain Intensity, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities [Patient-Reported Outcomes Measurement Information System (PROMIS) – Preference (PROPr)] • Satisfaction with telemedicine based opioid treatment (Treatment Satisfaction Survey) and patient centered care (Patient-centered care climate questionnaire) • Salivary drug screen (baseline only) • Sexual risk (e.g., type/frequency unprotected sex, # of partners; HIV risk screening tool)
	Clinical & Social services use *(per self-report and audits of the EPIC EHR "care everywhere" tool)*	• Buprenorphine treatment linkage and adherence (modified PhenX Treatment for Substance Use, self-reported medication dose logs) • Harm reduction and social service utilization (NMOS) • Satisfaction with AI-driven text messaging tool, NYC DOH pamphlets (i.e., control arm) and PRC support (Participant feedback survey) • PRC services use and patient-centeredness (OPTION scale for patient involvement)
	Psychological & Physical factors	• Depression (e.g., Hamilton Depression scale) and anxiety (Hamilton Anxiety Scale) • Quality of life/self-rated health (SF-12) • Pain: indicate pain on diagram; rate pain at its worst; medications receiving for pain; % relief from medications; how pain has interfered with life activities[8]

Table 1 references can be found in the Reference section of the grant.

Subject Payment

Participants will receive monetary incentives for their time spent on data collection procedures and other study related tasks. Additionally, they will be provided with snacks (granola bars, protein bars, jerky, etc.) and coffee during their participation. We will reimburse participants for their time and participation in study activities using the Greenphire ClinCard system or a gift card of the participant's choice (e.g., Target, Amazon). Participants in the study will complete surveys at baseline/point of study enrollment, and will complete follow-up surveys at 3 months, 6 months, and 12 months. We hope to increase participant retention in the study by increasing the subject reimbursement rate by $5 increments. Participants will receive $50 at baseline, $30 at the 3-month follow-up visit, $35 at the 6-month visit, and $40 at the 12-month follow-up visit. Additionally, participants will receive a roundtrip MetroCard valued at $6.50 each time they complete a survey. The MetroCard cards purchased from the NYC Transit Museum in Grand Central will cover roundtrip travel to complete surveys. We anticipate that some participants will be lost to follow-up. Thus, we intend to survey 252 individuals at baseline, 202 at the 3-month

follow-up visit, 172 at 6 months, and 155 at the 12-month visit. In Year 2, we will begin to hold in-depth interviews among 3 stakeholder groups (n=10 frontline providers, 10 administrators and 10 PWUO selected from among the survey participants randomized in intervention arm 1). The frontline providers and administrators will receive $75 for their time and is commensurate with the average of the combined standard salaries for social workers, physicians, and nurse practitioners.

We employ previously approved compensation structures to promote retention in study participation during the full longitudinal period. Payments will not be tied to primary outcomes.

	Year 1	**Year 2**	**Year 3**	**Year 4**
Baseline Survey ($25)	$25 x 44 = $1,100	$25 x 84 = $2,100	$25 x 84 = $2,100	$25 x 40 = $1,000
3-month Survey ($30)	$30 x 17 = $510	$30 x 68 = $2,040	$30 x 68 = $2,040	$30 x 47 = $1,410
6-month Survey ($35)	$0	$35 x 58 = $2,030	$35 x 56 = $1,960	$35 x 58 = $2,030
12-month Survey ($40)	$0	$40 x 28 = $1,120	$40 x 52 = $2,080	$40 x 52 = $2,080
Totals	**$1,670**	**$7,290**	**$8,180**	**$7,453**

Participants randomized to TAU will receive similar payments at the same time points as participants in the intervention arm-1 and arm-2 groups. At the completion of each of the follow-up sessions all participants are compensated for their time.

Proposed Analyses

Aim 1 is a 3-year RCT involving community and ED-enrolled Black / Latinx PWUO who will be screened and enrolled (N=252) **Primary outcomes** will be based on remote and/or in-person follow-up assessments at 3-, 6-, and 12-months and consists of self-reported linkage to primary care-based OUD services (i.e., time to initial receipt of buprenorphine in primary care). **Secondary outcomes** include durability of treatment effect at 52 weeks (e.g., continuous retention in OBOT with buprenorphine), receipt of social services, and longitudinal engagement with the proposed intervention (up to 26 weeks).

Our **primary hypothesis** is that the rate of linkage to OBOT, i.e., time to first buprenorphine prescription, will be highest among PWUO participants randomized to texting + PRC, followed by those randomized to texting only, then to TAU. To assess this hypothesis, we will utilize Cox proportional hazards (PH) regression to investigate differences in time to service linkage (in days) by intervention group. Cox PH regression is a method for investigating the effect of several variables on the time to a specified event[170]. Cumulative hazards functions for the intervention groups will be examined using Nelson-Aalen plots and use the supremum test which uses martingale residuals to check the proportional hazards assumption. If the assumption is violated such that there is no difference in the direction of the association but there is variation in the magnitude of the association, i.e., the hazards ratio (HR) changes over time, then the coefficient that we estimate for that covariate is akin to an 'average effect' over timepoints that are observed in a dataset and the Cox PH model will perform moderately. If the hazards cross, i.e., a change in the direction of the association, the Cox PH model will perform poorly, and we will extend the Cox model to allow for nonproportional hazards using time dependent covariates. Intervention group as assigned will be the sole explanatory variable in the models (see **Methodological Considerations and Alternatives**).

Secondary and exploratory analysis will rely on data collected at 3-, 6-, and 12-month follow-up surveys that will permit analysis of secondary outcomes of: (1) durability of treatment effect at 52 weeks (e.g., continuous retention in OBOT with buprenorphine); (2) engagement with social services; and (3) longitudinal engagement with the proposed intervention (up to 26 weeks). For these analyses, we will use generalized linear mixed effects regression to model binary outcomes indicating longitudinal engagement in 26-week treatment (yes/no) and continuous retention in buprenorphine treatment at 3-, 6-, and 12-months (yes/no) with no more than a 28-day gap in receiving an active buprenorphine prescription over each period. These models will include a participant-specific random intercept to account for the repeated-measures structure of the data.

Methodological Considerations and Alternatives: To assess whether randomization was successful, we will compare the distribution of demographic characteristics, PhenX consensus measures, medical/psychiatric history, technology use patterns, and risk behavior variables (see *Data Collection*) by intervention arm. Variables contributing to baseline imbalance will need to be included as adjustment variables in regression models.

Missing Data and Sensitivity Analysis will rely on ensuring that the model assumption of non-informative study dropout or missing at random is reasonable and avoid potential bias, we will compare dropout rates between intervention groups as well as other measured variables, e.g., medical/psychiatric history, technology use patterns, and risk behavior variables. If there is empirical evidence of nonrandom dropout, we will model the dropout event using available factors to identify and estimate their influence. To meet missing at random model assumption, variables that predict dropout will be included as auxiliary variables via multiple imputation.

Intervention fidelity is an important consideration with "real world" research interventions. Lack of fidelity can increase the possibility of a type I or II error and make study findings difficult to interpret. Certain study design considerations are incorporated to support intervention fidelity, e.g., use of a standardized, established training for PRCs, collection of important study measures like PRC-participant communication logs. In the data analysis, we will confirm that the intervention is received in the same way within each intervention arm across participants and through time by comparing type and frequency of topics discussed as well as process measures (see Data Collection); we will also compare fidelity metrics by participant characteristics. In the unlikely event that we do not observe an intervention effect, participant data on social determinants, risk behaviors, patient-centered care, clinical and social services use, and technology use will be instrumental in the interpretation of study findings and recommendations for practice.

The **sample size**, *N*=252, was chosen to provide sufficient power for analyses associated with the defined primary outcomes and accounting for 20% attrition. In the absence of normative data, based on results of prior studies among emergency department enrolled PWUO that indicate modest uptake of MOUD (~5%[191]), and completing referrals to MOUD services (~25%[192-194]), we compute the power to detect significant effects.

Aim 2: Can the multimodal intervention be equitably implemented in clinical care?

Aim 2 is designed as a study of multi-perspective stakeholder feedback (N=50) of our proposed multimodal intervention to inform how best to integrate this approach into care teams using the RE-AIM framework to guide the evaluation of the intervention[177–179]. Our sample size is driven by qualitative methods. We propose to recruit frontline providers (n=10), administrators (n=10), and a subset of PWUO participants randomized to intervention arm-1 (n=30) for a total N=50.

The RE-AIM and CFIR will be used as process and determinants frameworks that will allow us to adapt the intervention in arm 1 as it is unfolding, Additionally, they will be provided with snacks and coffee during their participation. and guide the evaluation of its effectiveness from the perspective of key stakeholder groups[197–199]. Specifically, we will assess intervention **R**each (among both PWUO and frontline providers); **E**ffectiveness (defined as PWUO linking with primary care-based buprenorphine treatment and social services, and as successful integration of PRCs in care teams); **A**doption (by providers and administrators); **I**mplementation (assessing fidelity of key implementation features and potential intervention adaptations during implementation, and resources and costs on a systems-level per administrator interviews and economic data analyzed in Aim 3); and **M**aintenance (assessing whether the intervention becomes integrated into routine practice, i.e., assessing the institutionalization of primary care-based buprenorphine treatment and social services (see *Table 3*).

We will complement RE-AIM with the CFIR to evaluate multi-level barriers/facilitators associated with intervention reach, effectiveness, adoption, implementation fidelity / adoption, and maintenance. The CFIR[76] specifies five main implementation determinants, including characteristics of the *Innovation* being implemented, the *Outer and Inner Settings* in which an intervention is being implemented, characteristics of *Individuals* involved with implementing, delivering, and/or receiving the innovation, and the implementation *Process*.

The RE-AIM and CFIR assessments will be based on the REDCap survey, EHR data (see *Table 2*), PRC communication logs and qualitative longitudinal interviews with PWUO, frontline providers (including PRCs), and administrators. These findings will capture data on the processes of intervention implementation as they occur, and the reasons why they unfolded in particular ways at the individual, interpersonal (e.g., PRC-PWUO), and system-levels (see below for details on Interview Guide).

Table 3. Implementation and cost-effectiveness measures within the RE-AIM framework

DIMENSIONS	MEASURES
Reach	Number, percentage, and representativeness of patients who participated in intervention
Effectiveness	Intervention impact on primary outcomes: percentage of patients linked to OBOT, non-study health service utilization (cost-offsets), health-related quality of life; and secondary outcomes: estimation of time to linkage, treatment days in OBOT, self-reported criminal justice involvement and activity (days incarcerated, criminal activity, arrests), social safety net services (unemployment income)
Adoption	Percentage / representativeness of providers / administrators engaged with intervention
Implementation	EHR data, survey data, micro-costing data on fixed and start-up cost associated with intervention, PRCs process notes, and downloaded text exchanges analyses to assess consistent delivery of intervention implementation
Maintenance	EHR data, survey data, micro-costing data on variable cost associated with intervention, PRCs process notes, and downloaded text exchanges analyses to preliminarily assess integration of the intervention into NYC Health+Hospitals system at end of data collection (time point 3).

Approach

In-depth qualitative interviews will be conducted remotely using the HIPAA-compliant WebEx platform or in-person for PWUO participants with limited internet access. A key feature of the stakeholder groups is the between- and within-group heterogeneity (i.e., varying roles in intervention/responsibility/authority) that will enrich the interview data feedback on the relevance and utility of the intervention. These findings will enable us to evaluate the multimodal intervention from multiple perspectives and thus, better tailor it to the needs of all key stakeholders. There is also heterogeneity within each stakeholder group that can enrich the interviews. For instance, we will interview providers across the hierarchy from PRC to clinicians, and administrators, whereas in the PWUO sample, we anticipate some variety in treatment histories, structural barriers to care, technology savvy, and importantly, involvement, perceived benefit, and longitudinal engagement with the intervention.

Key CFIR topics incorporated in the PWUO interview guide to contextualize experiences with the intervention will include: 1) the **intervention components,** including ease or complexity to use, advantages and disadvantages relative to previously utilized OUD services, compatibility with participants' daily lives, barriers to sustained engagement, and participants' interpersonal interactions with the PRCs; 2) experiences with the **inner settings** of the social and clinical service organizations that participants were referred to and/or engaged with during the intervention, including stigma/discrimination, perceptions of the culture- and person-centeredness of the settings, and perceptions of the structural barriers and resources available to meet their needs (e.g., inclusive eligibility for services, timely appointments, care coordination/linkages, trauma-informed clinic/office design); 3) the **outer settings** in which participants live, including neighborhood safety and social barriers that influence OUD and that influence engagement with OUD services (e.g., OUD stigma in the community, telephone/internet access, peer support); 4) **individual characteristics**, including histories of opioid use and overdose, accessing OUD and social services; and 5) the **implementation process**, including interactions with the study team for recruitment and intervention delivery, as well as recommendations for improving intervention reach, effect, fidelity/adaptation, adoption and maintenance to overcome barriers that are identified throughout the interview. Frontline provider and administrator guides will cover: 1) the **intervention components**, including their ease or complexity to be integrated into routine care, their advantages and disadvantages relative to implementing other programs, intervention adaptability to local contexts, costs, and modifications made during the project. PRCs will also provide feedback on interactions with PWUO participants; 2) the **inner settings** of the participating institution, including PRC integration challenges into care teams (from both the PRC and other providers' perspectives), leadership support for the interventions, the degree of fit between the intervention and institutional missions/values, and institutional challenges providing primary care-based buprenorphine treatment (e.g., administrative, resource-related obstacles); 3) the **outer settings** of participating institutions, including potential barriers/facilitators to promote intervention reach in primary care, regulatory barriers/facilitators towards delivering OUD services; and perceptions on how CSDH impacts PWUO and their engagement with OUD and social services; 4) **individual characteristics**, including perceptions of, and experiences with, providing care for underserved Black / Latinx PWUO; and 5) the **implementation process**, including interactions with MPIs for intervention training, and feedback for improving intervention reach, effect, fidelity, adoption and maintenance.

Data Analysis

The analysis of the qualitative interviews will begin alongside the data collection. This will enable the timely identification of intervention implementation limitations and enable course correction as the study is unfolding. The interview transcripts will be content analyzed using a 7-step process

developed over the years by our team[120,122,148,204]. This process allows for a systematic identification of subcode, codes and themes while keeping the data contextualized. Specifically, we will complete the following tasks: Step 1, identify the principal issues discussed by participants; Step 2, construct preliminary definitions of the analytic themes; Step 3, develop and apply core codes and subcodes to the initial set of interviews at each interview round. Blocks of text within text tagged with core codes will be assigned subcodes; Step 4, develop a provisional coding scheme; Step 5, test the provisional coding scheme by coding new transcripts; Step 6, reconcile coding differences and construct a final coding scheme; and Step 7, apply the coding scheme to the full dataset. Close reading of the coded interview transcripts will reveal data patterns withing each sample, but importantly, also highlight differences/similarities across the stakeholder groups that will inform intervention adaptation. For instance, an emerging qualitative data pattern midway through the data collection process (i.e., 6-month assessment) could be that PWUO are encountering regulation barriers and strongly recommend changes in guidelines that will afford them flexibility in enrollment and referrals to better engage PWUO in care. This lack of flexibility might also emerge in the administrators' interviews. This prismatic assessment of the intervention will enable us to draw inferences that will inform the refinement of the intervention as it unfolds. Qualitative findings from PWUO participants (N=30) will be analyzed in tandem with: a) the PRC notes on CSDH for these participants (i.e., the health habitus note); b) their electronic administrative data, EHR data (e.g., primary care missed visits); and c) their REDCap survey data (baseline, 3-,6, and 12-month follow up). For instance, we will analyze whether PWUO with numerous patient-initiated requests for telephone assistance from physicians (based on Participant Feedback Survey; a domain in the REDCap survey) who also report patient-centeredness will also be consistently engaged with the different features of the multimodal intervention. Such a triangulation of data conducted over time will inform intervention effectiveness and maintenance. Findings from the PRCs' interview data will be analyzed in tandem with: a) the downloaded PRC-PWUO participant text exchanges in intervention arm-1; b) the training and supervising notes of the MPIs as part of their PRC CSDH training and supervision; and c) notes from weekly research meetings pertaining to PRC experiences and their integration in care teams to add to the rigor of the intervention's assessment.

Intervention feasibility, fidelity and adaptation. Intervention feasibility will be assessed by examining fidelity to core components of the intervention (e.g., linkage to primary care-based buprenorphine treatment) and implementation strategies (e.g., training for PRCs in cultural and structural humility). Importantly, we will also examine any necessary intervention adaptations and the reasons for these changes, via the qualitative interview analysis. Again, we will employ different forms of data, including the PRC-PWUO participant text exchanges. Specifically, 10% of PRC-PWUO participant text exchanges will be reviewed among participants (n=25) providing written consent to this process to assess for consistency with CSDH-focused CSH training principles during the first two months following enrollment. Intervention fidelity will also rely on periodic reviews of the PRCs' notes to determine if they have elicited the cultural and social barriers and facilitating factors influencing PWUO engagement with services and how they are integrating these insights into their text exchanges with participants. Lastly, three cycles of in-depth interviews with administrators, frontline providers including PRCs and PWUO participants in intervention arm 1 will assess intervention implementation as it unfolds in real time and inform modifications to the AI-driven texting algorithm and/or PRC training. The risk of contamination across intervention conditions is minimal given its technology mediated nature. However, to minimize this risk, study participants will be asked not to share any study content or experiences with peers. Potential contamination will also be assessed by asking participants if they heard about the study or knew any participants prior to entry.

Aim 3: How Cost-Effective is the multimodal intervention?

Aim 3 is an economic evaluation of the proposed multimodal intervention using well-established guidelines of prospective economic evaluations alongside clinical trials.[102,194,195] Outcome measures will be analyzed using multivariable generalized-linear mixed models (GLMMs) to adjust for potential confounding factors and the skewed distributions commonly associated with healthcare cost data and censored outcomes (e.g., QALY).[195] The GLMM, an extension of the GLM, allows the most appropriate mean and variance functions to be chosen based on the observed data,[195] as well as for the inclusion of random effects.[202] The primary outcomes for Aim 3a will be the **budget impact tool consolidating the resources and associated costs required to implement and sustain** the PRC-participant text contact + interactive text messaging, and interactive text messaging only interventions compared to TAU. The primary outcome of Aim 3b will be **the incremental cost-effectiveness ratio** (ICER),[194,195] defined here as the incremental mean cost between the two intervention arms and TAU divided by the incremental mean effectiveness (QALY and OUD treatment days) of the two arms calculated separately. HRQoL is increasingly recognized as a key indicator of patient well-being that is not captured in clinical measures. The QALY is a measure that combines the HRQoL associated with an individual's health state and their time spent in that state.[102,194,195] The **QALY is recommended as the primary effectiveness measure in economic evaluations** due to its ability to be compared across interventions and disorders, and its association with commonly-accepted value thresholds (i.e., cost-per-QALY).[194,195] **OUD treatment days is an important continuous measure of effectiveness for clinical stakeholders** and calculating cost-per-OUD treatment days enables comparisons with prior published economic evaluations of OUD interventions reporting similar clinical effectiveness measures.[112] As part of the process of estimating ICERS, we will be able to test the 6- and 12-month post-intervention differences between arms of a) the average total costs to the healthcare sector, state policymaker, and society by resource categories; and b) the average QALYs and OUD treatment days; thus, two ICERs will be calculated for each of the three stakeholder perspectives for each of the aforementioned evaluation periods.

Health Economic Measures

Health-Related Quality of Life (HRQoL) will be measured using the validated Patient-Reported Outcomes Measurement Information System (PROMIS)–Preference (PROPr) instrument.[232–234] PROMIS (including PROPr) was developed using item response theory (IRT), with support from the NIH. Because of its IRT foundation, PROPr is more flexible, and improves upon common deficiencies of alternative HRQoL instruments.[235] The PROPr scoring system uses the respondent's scores for each of the following domains to calculate a HRQoL index value that represents the general US population's preference for a respondent's health state: Cognitive Function–Abilities, Depression, Anxiety Fatigue, Pain Interference, Pain Intensity, Physical Function, Sleep Disturbance, and Ability to Participate in Social Roles and Activities.[236,237] HRQoL values produced by PROPr range from -0.022 to 1, where 0 represents death, 1 represents perfect health, and values below 0 represent states perceived to be worse than death. The HRQoL value is then used to calculate regression-adjusted QALYs per study arm as our team and others have done in similar studies.[103,122–125,238]

Healthcare, Non-Medical and Other Services. The utilization of healthcare services by participants will be measured using study data and the Timeline Follow-Back (TLFB)[191] methodology via the Non-study Medical and Other Services (NSMOS) form. Healthcare services will include inpatient, outpatient, telehealth, and ED services; opioid use disorder treatment

medications, and residential and outpatient substance use disorder treatment days; hospital detoxification days; and mental health treatment visits. The reliability and validity of self-reported data is well established over recall periods similar to those in this proposal[196,204,239–241]. Non-medical and other resources required to determine the costs from the state policymaker and societal perspectives (e.g., recidivism, workplace productivity, etc.) will be collected via the NSMOS form, Addiction Severity Index – *Lite* (ASI), and other study instruments. The NSMOS, ASI, and other study instruments have been successfully used by the economic team in prior economic evaluation studies[122,124,125], and is currently in-use in numerous clinical trials of substance use disorder treatments, including those associated with the NIDA Clinical Trials Network (CTN) and Justice Community Opioid Innovation Network (JCOIN)[120,123,242].

Aim 3 Data Analysis

Aim 3a will involve the development of a customized budget impact tool using implementation-related data collected by the trial to capture all relevant healthcare resources (see "Intervention Costs") following recommended methods.[200] The resource-costing method will be used to value all relevant, non-research resources. Resource costing involves determining a per-unit price-weight for each relevant resource and multiplying the price-weights by the number of resource units utilized. The budget impact tool will include 5 Microsoft Excel worksheets, with drop-down menus incorporated throughout to increase ease of use, and limit data-entry errors. The first worksheet is a dashboard that is automated by linking data from the other worksheets and displays the total costs differentiated by resource category identified in the microcosting analysis (see Intervention Costs). The remaining worksheets include the various resources that could be associated with different OUD treatment models, and their associated unit costs. Thus, users will select the quantity of each relevant resource, change the unit costs if desired and be able to view detailed cost estimates by fixed, variable, and time-dependent components.

Aim 3b. Separate multivariable GLMM regressions will be used to estimate predicted mean costs for all resource categories (see healthcare resource utilization, non-medical and other resources), according to each stakeholder perspective, and then summed with the intervention costs (see Intervention costs) to calculate total costs. Thus, the GLMM will be used to estimate predicted mean effectiveness measures by study arm for months 6 and 12 after randomization. Final predicted costs and effects will be generated using the statistical method of recycled predictions;[195] and these values will then be used to construct estimated ICERs and cost-effectiveness acceptability curves will be constructed (see Cost-effectiveness Acceptability Curves) to illustrate the probability that a given intervention is cost-effective across a range of value thresholds (i.e., cost-per-QALY gained, and cost-per-additional day of OUD treatment).[195] Results will also be disaggregated by sex; for example, research by our CHERISH colleagues suggests that outcomes derived by measures of HRQoL (i.e., QALYs) differs by sex among individuals receiving medication treatment for OUD.[203] P-values and 95% confidence intervals will be estimated using nonparametric bootstrapping techniques within the multivariable GLMM framework,[195] to account for sampling uncertainty.

Determining Cost-effectiveness. A health intervention is considered cost-effective if the value of the ICER falls below the stakeholder's willingness-to-pay value for each unit increase in effectiveness measures (QALYs, OUD treatment days). We will determine if PRC-participant text contact + interactive text messaging, and/or interactive text messaging only is cost-effective compared to TAU using the generally-accepted willingness-to-pay threshold range of $100,000 - $200,000 per QALY gained[204], and evaluate the confidence of that assessment by calculating the **cost-effectiveness acceptability curves** (CEAC).[205] The CEAC displays the probability that the ICER would fall below a given willingness-to-pay threshold, i.e., the likelihood that the intervention

is considered cost-effective, across a range of values per QALY and treatment outcomes. We will calculate CEACs using the distribution of cost and effectiveness parameters obtained from the recommended non-parametric bootstrap procedure.[102,195, 201]

Missing Data and Sensitivity Analysis in Aim 3b will be addressed using recommended approaches for prospective economic evaluations conducted alongside clinical trials,[195] and combining such methods within the nonparametric bootstrap based on our recent work.[201] We will also conduct extensive sensitivity analyses to account for uncertain precision in assumptions and parameter estimates applied in the analyses.[102] For example, we will test the robustness of the results as they pertain to variations in unit costs, and values estimated using the more robust and efficient GLMM regression will be compared to those estimated using the more transparent ordinary least squares regression, as well as to the unadjusted mean values.

Study Population

Recruitment

Emergency department and community recruitment of Black / Latinx PWUO in Aim 1 will involve identifying potential study participants with opioid use disorder (OUD). A sample of 252 community and ED-recruited Black and Latinx PWUO will be recruited over a 2-year period and followed for a duration of 12-months with purposeful recruitment of male: female adults along a 2:1 target ratio (169 males: 83 females) and a target minimum 25% aged 18-29 (see *Figure 1*).

Planned

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	42	84	21	43	189
White	0	0	21	42	63
More than One Race	0	0	0	0	0
Total	42	83	0	0	252

Potential study participants approached by the study team will be informed of study details, undergo informed consent, complete baseline REDCap assessment, and will then be randomized (1:1:1) using a random block design (block sizes 3, 6, 9) to 1 of 3 study arms, stratified by gender. Finally, participants will be compensated for their time at visit end and given an appointment schedule for in-person or remote survey visits. Randomly selected participants from intervention arm 1 (n=30) will be invited for the qualitative implementation interviews (see Aim 2). All randomized participants who need a phone will be provided one by the study and tracked over time by leveraging Drs. Lewis', Lee's, and Tofighi's expertise in the event of changes to mobile phone numbers.

Participants will be given instructions to complete remote or in-person follow-up assessments that will be conducted in one of three data collection sites. *All* potential participants will complete informed consent, computer-assisted baseline survey, will be administered the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) for OUD by Dr. Tofighi to differentiate between participants with OUD versus individuals misusing opioids to quell untreated pain symptoms only. Next, participants will be randomized (1:1:1) following a random block design (block sizes 3, 6, 9) to interactive texting + Peer Recovery Coach-supported text contact, interactive texting only, or TAU, and include stratification by gender.

Our proposed recruitment schedule is highly feasible since prior NIDA-funded trials involving recruitment of vulnerable persons who use opioids and other illicit substances in the identified

hospitals resulted in successful enrollment of study samples ranging from 180 - 200 ED-recruited participants annually, as well as timely completion of all study timelines. As in our previous work, participants will be recruited in-person by study staff.

Study posters and flyers will be developed for distribution in the emergency department using input from our entire study team and the NY Statewide Multicultural Advisory Committee in which NKI-CCASE has active membership, and comprised of 30-40 behavioral health community stakeholders, each representing socially and culturally diverse backgrounds. This committee advises the NYS Office of Mental Health on cultural relevance and appropriateness of evaluation and training tools, training curriculum, research and practice protocols, and new and existing patient/client programs as it relates to representation of diverse populations based on race, ethnicity, gender identity, sexual minority identity, and spoken language.

Eligibility Screening and Enrollment: We anticipate most interested participants will undergo a brief in-person 10-minute screener using a mobile application that affords sufficient privacy. Once eligibility is determined, study details will be explained to the participant and will be given instructions for study enrollment upon discharge from the emergency department, including completion of informed consent, baseline assessment (REDCap), DSM-5 for OUD checklist, followed by randomization. Participants will receive $25 at baseline, $30 at the 3-month follow-up visit, $35 at the 6-month visit, and $40 at the 12-month follow-up visit. Participant compensation will be delivered via timely deposit to a reloadable debit card using the Greenphire ClinCard system, which we have used in both past and ongoing projects. This system allows for timely reimbursement of participants completing remote study visits.

Alternatively, we will provide interviewer-administered computer-assisted REDCap follow-up surveys virtually (video or phone) to ensure optimal convenience for study participants by mitigating unanticipated barriers to study visit completion. Study participants will also be provided with addresses to follow up at any one of the three study offices that is most desirable for participants.

Finally, all PWUO study participants who screen eligible will be characterized on a screening contact log sheet which will indicate gender, race/ethnicity, and opioid type which will provide data to help gauge those who follow through with study enrollment vs. those who are lost between screening and enrollment, baseline, and randomization follow-up visits. This information will inform final results of the study with respect to the representativeness of our study sample and provide insights to the intervention’s reach (key implementation feature).

Of note, a select number of PWUO will be drawn from the Aim 1 study participants who were randomized to the PRC-supported text contact + interactive text messaging intervention arm-2 (n=30) to participate in in-depth interviews in Aim 2 lasing approximately 60 minutes. For Aim 2, the inclusion and exclusion criteria for PWUO participating in the in-depth interviews (Aim 2) are identical to those for Aim 1, since we will recruit a subset of participants randomized in intervention arm-1 (n=30).

Inclusion/Exclusion criteria

PWUO Study Participants

Inclusion criteria: 1) ≥18 years of age; 2) fluent in English; 3) self-reported non-prescription opioid use <30 days prior to consent; 4) provision of informed consent; 5) planned stay in NYC ≥12 month; 6) Black and/or Latinx race/ethnicity; 7) positive urine toxicology for opioids per EMR records or study staff administered random saliva drug testing; 8) diagnosis of OUD per the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5); 9) self-reported interest in initiating buprenorphine in primary care, or elsewhere; and 10) must have a mobile phone data plan.

Exclusion criteria: 1) inability to comprehend text content written at a 3rd grade reading level; and 2) physical or visual disability preventing mobile phone use

Retention Plan for PWUO in Aim 1 centers around methods previously utilized by the MPIs in their prior NIH-funded studies that have yielded rates of study retention above 80%. Components of our planned participant retention strategy include: 1) Completion of a locator form at baseline and at all follow-up visits to assist in locating participants in the event of a missed study visit (e.g., participant's current address, email, phone numbers, contact information for at least 3 trusted friends/family); 2) soliciting consent to contact the participants' 3 trusted contacts as well as health care staff at the study site hospital; 3) providing timely study visit telephone call and text reminders; and 4) coordination with trained study staff to conduct outreach to assist with in-person searchers at their homes, shelters, or other community sites. On the day of a missed study visit, the participant will receive two phone calls and two text messages at different times of the day. If there is no response within 24 hours, mailed follow-up reminder letters and/or emails will be sent encouraging contact with research staff. If there is no contact within 72 hours, the participant's locators will be contacted at varying hours. Study staff will also check for incarceration status using http://www.vinelink.com/, and google.com, intellius.com, and spokeo.com for updated contact information. All contact with participants and/or their locators will be documented in the Participant Communication Log. No information from this form will be used in data analyses. Participants will be offered incentives to respond in-person or via telephone to ensure improved retention during scheduled study follow-up visits.

Projected attrition rates

Projected patient attrition rates for the 12-month study duration are presented in the table below. Note that these conservative attrition rates are higher than those we have observed in past cohorts engaged with our intervention. We estimated the greatest 'attrition' between Intake and Month 1, as participants may consent and decline to participate in follow-up assessments or decline to continue engagement with the intervention(s).

Intake	**Month 0**	**Month 3**	**Month 6**	**Month 12**
Attrition %	--	20%	15%	10%
Sample retained (N)	252	200	170	153

Frontline provider and administrator participants in Aim 2.

Recruitment of Providers, Administrators, and PWUO in Aim 2 will comprise 50 total stakeholders who will represent 3 groups including providers (n=10), administrators (n=10), and PWUO (n=30) to undergo in-depth interviews to assess implementation and scale-up upon completion of the trial.

Provider and administrator stakeholders will be enrolled from partnering hospitals and health systems. Frontline providers (PRCs, DEA-waivered buprenorphine prescribers, behavioral health, and social service providers) and administrators (i.e., departmental supervisors and health systems leadership) will be recruited for Aim 2 during the second quarter of Year 2 through the end of the third quarter in Year 4.

The study team will also approach staff employed in outpatient OUD services programs (e.g., opioid treatment programs, office-based opioid treatment) who provide methadone and/or buprenorphine treatment. Providers will be recruited by full-time research staff working onsite conducting study activities.

Inclusion Criteria

Frontline provider and administrator: current affiliation with the collaborating hospital or hospital system as a DEA-waivered buprenorphine prescriber, and social service provider working with PWUO, or departmental supervisors and hospital leadership responsible for programs and policies on OUD services.

Inclusion Criteria

1. Licensed prescriber or administrator employed by the respective site, or at a clinical partner of the respective site, where they will act as participants and be part of the treatment team
2. Currently practicing in the treatment of OUD with either Buprenorphine or Methadone;
3. Able to speak, read, and write English fluently and to provide informed consent in English

Exclusion Criteria

None

Informed consent

Patient Participants

All OUD patients will be consented by the research coordinators, with research training approved by the IRB (see **sIRB Plan**). If participants indicate willingness to be contacted by research staff, they will be given the opportunity to read the informed consent document and/or review the document with staff.

Clinician and Administrator Participants.

All providers will be provided with written consent by research staff to participate in the study. They will be given the opportunity to read the informed consent document and discuss any potential concerns with staff.

Inclusion of Women and Minorities

Our study will enroll women and Black and Latinx adult persons who use opioids (PWUO). Opioid overdose deaths among Black / Latinx PWUO are disproportionately higher despite historically lower rates of opioid use disorder (OUD) compared to White PWUO. There are fewer available providers prescribing medications for OUD in underserved Black and Latinx communities. Finally, Black and Latinx patients initiating buprenorphine for OUD in emergency department settings experience higher rates of loss to follow-up relative to their White peers. Hence, the proposed study will focus on community and ED-enrolled Black and Latinx PWUO who carry the highest burden of OUD and opioid overdose events. We will use venue-based and street outreach in spaces where opioid-related overdose rates are highest, and in neighborhoods where harm reduction services are located.

This study will set a target enrollment of 33% women who use opioids. Women experience lower rates of opioid use disorder (OUD) treatment utilization versus men since services fail to tailor care for women, particularly underserved Black and Latinx women, so their inclusion is critical. However, the proposed 2 : 1 ratio (male:female) reflects the distribution of illicit opioid use by gender. The proposed multimodal intervention (i.e., AI-driven texting tool, peer recovery coach-supported text contact) is also suited to address social determinants of health experienced by women with referrals to housing, peer support groups, reentry support among criminal justice involved women, domestic violence support groups, legal aid, medical services, employment training, and other services tailored to underserved women with substance use disorders. No PWUO will be excluded or included based on gender identity regardless of biological sex at birth.

Study Procedures: Patients

All Patients

Day 0

1. Subjects will be enrolled and consented in person.

2. All subjects will complete the following surveys before randomization (3 hours to complete): ***Demographic and CSDH characteristics***[172]; and ***PhenX consensus measures***, including the Addiction Severity Index[174], Risk Assessment Battery (RAB)[279], fatal and non-fatal overdose episodes[177,178], Disparate Health Care Quality[179], intersectional opioid-related stigma[180], Everyday Discrimination Scale,[181] mobile use characteristics and Medical Outcomes Study Social Support Survey[183],

   Table 2 includes REDCap survey data definitions and variables, including:
   - Demographic instrument (age, race, ethnicity, veteran status, legal history, type of residence, employment, education);
   - Sociocultural & demographic determinants of health;
   - Clinical interview to ascertain medical and psychiatric/addiction history (family substance use history, primary, secondary and tertiary substances, pattern and severity of substance use, treatment history, individual and family medical history, current health status, prior and current medications, and psychiatric symptoms);
   - Substance use and sexual risk behavior;
   - Clinical and social services use; and

3. Participants randomized to Intervention arms-1 and 2 will have their phone numbers entered in the AI texting software dashboard. The AI-driven texting goals, operational sequences, and content have been iteratively refined in numerous studies among Black/Latinx PWUO to ensure optimal adoption (see *Table 1*)[129,131].

   Text content are based on federal and consensus guidelines on optimizing medical management for PWUO with buprenorphine[167,168], and addressing CSDH[169–171] and include:
   a. CSDH content, delivered once/day, include: (a) stigma-reduction (e.g., internalized and anticipated stigma); (b) social resources identified in our community resources & services scan (e.g., peer support groups for PWUO and other minoritized groups); (c) educational resources (e.g., GED, vocational training); (d) economic stability (e.g., public assistance, employment / vocational services, transportation vouchers); (e) food security (e.g., food stamps, food pantries, subsidized farmers markets); (f) free legal aid; and (g) emergency housing.
   b. Harm reduction content, sent 2x/week, includes opioid overdose prevention training, instructions linking with primary care to receive opioid overdose education, naloxone, and instructions to access city-wide harm reduction sites offering sterile syringes, naloxone, and supervised injection services if desired;
   c. Motivational enhancement content, sent 3x/week, encourage uptake of OBOT services by *evoking* self-motivational replies and commitments to text prompts, *building motivation for planned* uptake, *establishing a plan* for uptake, adopting *treatment adherence and maintenance strategies* after confirming uptake per text queries, and applying coping strategies for high-risk situations that may precipitate the risk of illicit use;

d. Medical Management content tailored to OBOT *after* confirming entry in treatment using 2x/week text "check-ins". Text categories will consist of: (1) **Support during induction and stabilization to buprenorphine** that targets *buprenorphine adherence* and *self-management* with a once daily text at 9:00 am assessing for withdrawal symptoms. For a "*Yes*" response to withdrawal symptoms, participants will receive: (a) instructions on buprenorphine and/or comfort medication administration; (b) query for continued opioid use; and c) repeat queries at 12:00pm and 6:00pm for cravings and withdrawal symptoms. If participants report "*Yes*" to opioid use, they will be informed of the risk of overdose and may request a physician phone call during regular clinic hours (i.e., *patient-provider communication*); (2) **Appointment adherence** "tips" (e.g., setting written/mobile phone calendar reminders) that enhance *self-management* sent 1x/week; (3) **Supportive content** comprise alternating messages between *medication adherence* (e.g., buprenorphine), *reinforcement of reducing harmfui substance use*, or *12-step meeting and counseling participation* (i.e., hotlines, meeting sites / schedules, free online resources); (4) **Educational content** that enhance *self-management* with medication dosing, side-effects, overdose prevention, and online public-facing resources;
e. Instant help *allows participants to query* the texting software and receive personalized motivational enhancement, educational, or clinic/social services contact details via menu items and open-ended queries captured by natural language processing to enhance *patient-physician communication*.

Table 1: Artificial intelligence (AI)-driven text message content and delivery protocol

Text content	Content domains	Frequency	Content examples
Motivational enhancement content	Encouraging of harm reduction and MOUD service uptake	x3 per week	It's the small steps that make the biggest change. Get sbx, naloxone, or counseling @6466946821
Harm reduction	Encouraging harm reduction service uptake	x2 per week	Check this 4min vid youtu.be/PMGVNlcpAk &be a lifesaver. reply "1" to get a free televisit or Narcan
Educational content	Information regarding harm reduction and MOUD services	x3 per week	Tell a friend: Getting narcan or HIV/Hep C testing is free & confidential. Call 646-694-6821 for free testing and treatment
Instant help option	Menu option to access all listed components	Participant driven	How can I best help? Reply with questions or hit "1" for clinical issues, "2" for social services issues, or "3" for ur peer coach
Social determinants of health	Menu option to access listed services	X2 per week	Tough taking care of your health if ur hungry or on the streets. Call us asap @6466946821 to get setup with services mon-fri 9-5pm
Stigma reduction	x2 per week	x2 per week	Whatever u need, u got a right to get a free check-up, treatment, or harm reduction. Reply "1" for more info. We got u!
	Medical management components **post-initiation** on MOUD	**Frequency** Induction/ Maintenance	**Content examples**
Supportive	Self-management, physician-patient contact	Daily x1 per week	Its easier to stick with the daily meds than restarting it all over. Is ur current dose helping? Reply "1" if yes, "2" if ur feeling sick or cravings
Educational	Self-management	Daily x1 per week	Its best to take your full dose in the AM. Avoid using it for anxiety or sleeplessness
Appointment reminders	Self-management	x2 per week	Your next appt at Bellevue is 01/01/2016 at 9:00. Call 212-562-1862 to reschedule
Harm reduction	Self-management	x2 per week	Friend using while in treatment? Mixing can take a life. Reply "1" for ez tips on saving a life

Intervention Arm-1. Individuals (n=84) will be assigned to receive *AI-driven CSDH-enhanced texting **and** PRC-supported text-based care/services coordination*. ***PRC-supported text check-ins*** to participants (3x/week) will be provided by 2 PRC study staff *in addition to* automated AI-driven texts in *intervention arm-1.* The PRC will personalize text "check-ins" to participants based on: (a) baseline CSDH needs (e.g., food insecurity, legal aid); (b) initial intake visit in primary care or challenges with service entry; and (c) content outlined in the CSH training addressing emerging participant challenges. The **CSH training** comprises a self-guided (45 minutes) and remote, live segment (2.5 hours) provided by Drs. Lewis, Lekas, and Pahl[70], focusing on how to build rapport, establish meaningful boundaries, and infuse their interactions with participants with insights regarding participant health habitus (i.e., tendency to care for health and wellbeing in certain ways) and its sociocultural determinants that hinder engagement in care (e.g., addressing internalized, anticipated, and experienced stigma, generating cultural and structural humility and self-reflection, and bolstering navigation skills). Any clinical challenges will be deferred to Drs.

Tofighi and Lee (e.g., linkage to OUD services). PRC text exchanges with participants will take place during regular hours (M-F, 9-5pm). If participants query PRCs with any clinical / CSDH challenges, PRCs will contact participants once daily to help support participants in resolving barriers. The PRC will log text interactions focusing on participant sociocultural barriers or resources (i.e., health habitus notes) that will inform Aim 2 as such interactions have been found to be an effective approach to services engagement among persons with OUD[72].

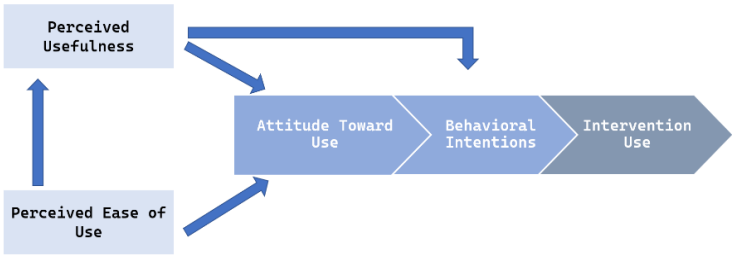
The **intervention fidelity of PRC text contact** is critical with real-world studies to reduce the risk of a type I or II error. Study design considerations are incorporated to support intervention fidelity (e.g., use of a standardized, established training for PRCs, collection of key study measures like PRC-participant communication logs). In the data analysis, we will confirm that the intervention is received in the same way across participants and through time by comparing type and frequency of topics discussed as well as process measures. We will also compare fidelity metrics by participant characteristics. In the unlikely event that we do not observe an intervention effect, participant data on sociocultural determinants, risk behaviors, patient-centered care, clinical and social services use, and technology use will be instrumental in the interpretation of study findings and recommendations for practice.

Intervention Arm-2 participants will receive the *AI-driven CSDH-enhanced text messaging only* (as described above; see *Table 1*). Participants in this arm (n=84) *will not receive text support from the PRC.*

Intervention Arm-3 (Control). Individuals randomized to the control arm (n=84) will receive treatment as usual (i.e., verbal instructions and NYC Dept of Health pamphlets detailing access to OUD and social services). No services will be provided except for social/clinical service referrals given at the end of each REDCap visit.

During follow-up at months 3-, 6-, and 12, the ***REDCap Survey*** will capture the domains listed above at enrollment (see Table 2) as well as the Technology Acceptance Model[187] (see *Figure 2)*: ***perceived usefulness, perceived ease of use****,* ***attitudes****,* ***behavioral intentions****, and* ***intervention usage***. In addition, data for each of these components will be derived from: the texting software (e.g., rate of participant responses to software-initiated text queries, number of participant-initiated requests for physician telephone assistance[53,129,188,189]), and through ***PRC communication logs*** and ***qualitative interviews*** to inform fidelity, implementation, and contextualize intervention efficacy, enhancing RE-AIM and CFIR frameworks.

Technology Acceptance Model (Figure 2)



Participant Discontinuation, Follow-up

Follow-up will establish one of the following conditions as the cause of discontinuation:

(1) Participant failed to return to clinic and unable to contact
(2) Participant terminated due to practical problems (no childcare, transportation, other)
(3) Participant moved from area
(4) Participant incarcerated
(5) Participant terminated due to AE/SAE
(6) Participant terminated for other clinical reasons
(7) Participant had a significant psychiatric risk (suicidal, homicidal, psychotic)
(8) Participant withdrew consent
(9) Participant deceased
(19) Participant terminated due to protocol deviation
(99) Participant terminated for other reason

sIRB Plan

The single IRB of record for this human subject research study will be the WCG IRB, which serves as Friends Research Institute's IRB. FRI has established a partnership with the WCG IRB to serve as the IRB through a master services agreement. Acting as single IRB – the Friends Research Institute and the WCG IRB is authorized through a dual use agreement with all sites referenced below.

The collaboration with Nathan Kline Institute, NYU, and Cornell will all be able to approve, seek modifications, and monitor research activities related to community enrollment and referrals to clinical or social services. The FRI and WCG IRB also has the authority to suspend, place restrictions on, or terminate approvals of research activities that fall within its jurisdiction that are not being conducted in accordance with IRB requirements, or that have been associated with unexpected serious harm to subjects.

WCG IRB is registered with the Office for Human Research Protections (OHRP and FDA) as IRB00000533. The Friends Research Institute holds a federal-wide assurance (FWA), 0002948. The FWA is an assurance of compliance with the federal regulations for the protection of human subjects in federally-funded research. All institutions/sites/organizations that will rely on the Friends Research Institute and the WCG IRB in this study will also be required to maintain a FWA throughout the course of the study.

Research Sites: FRI, NYU, Nathan Kline Institute, and Cornell.

All participating sites, prior to initiating human subject research activity, will sign an authorization/reliance agreement that will clarify the roles and responsibilities of the sIRB and participating sites. Sites will be required to sign an agreement before the sIRB review will commence for that site. Any sites added after award must also rely on the sIRB.

General Communication with sIRB and sites

The Friends Research Institute and WCG IRB will maintain records of the reliance agreements with all sites and will identify and document key communication roles. All communication with sites regarding sIRB policies, decisions and requirements will be communicated directly to the participating site's principal investigator and any other entities as referenced in the reliance agreement.

Information related to specific communications will be outlined in a detailed communication plan and will address the responsible parties for the following areas of communication:

- Local context information
- Local context review
- Conflict of Interest review
- Ancillary reviews
- Study team training
- Study team qualifications
- Study Wide IRB submissions (initial, continuing, reportable events and modifications)
- Site IRB submissions (initial, continuing, reportable events and modifications)
- IRB Determinations
- IRB Approved Documents

- IRB Policy Review
- Reporting Unanticipated Problems, Suspensions and Terminations

Study Research Infrastructure.

There will be six collaborating research sites in this study, Friends Research Institute, Nathan S. Kline Institute (NKI), NYU, Weill Cornell Medicine, NYC Health+Hospitals Lincoln Hospital Center, and START Treatment and Recovery. Each site and collaborating investigator will be responsible for all study procedures, including but not limited to recruitment, consent, data collection, analysis, and data storage. Community and ED-enrollment of potential PWUO participants will rely on CITI-trained study staff responsible for conducting on-site research activities including administering written consent, baseline assessments, and providing instructions for follow-up study visits.

WCG will serve as the IRB of Record for the study and therefore, it will review and approve all protocol documentation, and be responsible alongside the MPI for review and approval of any updates, revisions and for reporting and addressing any adverse events should they occur. Moreover, a master dataset with personal identifiable information will be maintained by the study coordinator at FRI.

Data Safety and Quality Assurance

The investigators will meet quarterly with the Data and Safety Monitoring Board (DSMB) to ensure the periodic review of study procedures, study data, and progress to ensure optimal participant safety. These meetings will allow DSMB members to make recommendations to the study investigators concerning the continuation, modification, or termination of the trial. The proposed DSMB plan will ensure optimal oversight and privacy safeguards for all participants by including individuals with extensive expertise in health information technology research and trials enrolling vulnerable populations.

Materials*:* All devices and platforms utilized by the study team will be password- and virus-protected with regular software updates and periodic mandatory changes of passwords. Study devices (i.e., tablets) will be encrypted, and data transfers will occur through secure file transfer between FRI server-maintained computers to NKI server-maintained computers (both accessible by each MPI).

Sources of participant data in **Aim 1** will rely on 3 sources of administrative data which will derive from study records (i.e., PRC-PWUO participant contact logs), the text message software communication logs, and for exploratory purposes only, the Hospital EHR. Data will be documented as follows: (1) process measures captured in PRC-PWUO participant contact logs (i.e., proportion of PWUO participants replying to PRC queries, PWUO participant queries to the PRC, topics discussed, actions required to address PWUO participant queries); (2) process measures captured in the text messaging software communication logs (i.e., messages sent to patients, percent of text queries that generated a participant response); (3) technology use patterns from the system level point of view (i.e., rates of mobile phone ownership, mobile phone turnover, mobile phone number turnover); and (4) receipt of OBOT or other OUD services elsewhere will be identified in the EHR and follow-up assessments (OBOT clinic appointments and visits completed, buprenorphine and/or naloxone fill/refill data). PRC-PWUO participant contact logs will be completed on computer-based forms using REDCap. The hospital EHR will

also be utilized on an exploratory basis to provide records data on: (1) OUD treatment / prevention retention data (i.e., weeks-in-treatment); (2) abstinence (i.e., proportion of opioid positive urine samples, overtime); (3) adherence to buprenorphine (i.e., buprenorphine positive urine samples); and (4) health outcomes (e.g., specialty care clinic visits data, including diagnoses, symptomology, treatment).

Privacy provisions pertaining to the AI-driven text messaging platform and software specifications are aligned with FRI, NIH, and federal guidelines and will be strictly adhered to, including mandatory Security Awareness and HIPAA training of all employees involved in the proposed study, including mandatory GCP training for all clinical trials staff, which includes Protection of Human Subjects training. All staff must sign a confidentiality agreement upon employment. FRI meets or exceeds all HIPAA requirements. For instance, faculty and staff are prohibited from keeping any clinical data, including clinical research data or study participant communication and metadata on their desktop computers; instead, it is stored on servers residing in the secured off-site data center. Transaction logs and database backup procedures allow the recreation of a clinical study at any point in time. All data for this project is stored in a secured database, only available to the study team. Amazon Web Services (AWS) Lex uses HTTPS protocol to securely communicate with clients (encryption in transit) as well as between services. Access to services are API-driven and tied to NYU user credentials via IAM privileges (see *Figure 1*). FRI has strict security policies to ensure the privacy and confidentiality of data and to guard against physical, accidental, or malicious loss of data or the hardware on which it resides. All resources, including web, database, and file servers, are protected from outside intrusion by a firewall that blocks unauthorized access to the LAN by any unauthorized user originating from the Internet, using a sophisticated combination of secure application proxies and packet filtering. Internal network security is maintained through Active Directory authentication. Intrusion detection software is employed to scan for attempted break-ins. User IDs and passwords are assigned and controlled as per SOP, and users are required by the system to change their passwords regularly. Access to clinical trials or other sensitive data is strictly limited and is granted only by the Director, Technical Support Unit. Such access is controlled by easily identifiable group policies.

Minimizing participant re-enrollment and quality assurance: As there is potential for a participant to enroll in the study more than once, we will take steps to minimize this occurrence. First, all participants will be asked to provide their name, phone number, birth date, and later, will be asked for identification such as the NYS Benefits ID card, driver's license, or any work identification cards. Prior to enrollment, prospective participants' names will be checked against this master database which will be merged at least weekly. While these efforts may not fully protect against duplicate enrollment, they will greatly minimize this occurrence.

Strict security procedures will help ensure confidentiality/security of data. Any data transference between FRI and NKI will be conducted by the study team using a password protected device as mandated by the IRB. Any hard copy study documentation will be kept in locked files in the offices of the MPIs at FRI. Personal identifiers will be collected and saved on a HIPAA-compliant server and kept separate from the data. All devices, software platforms, and mobile phones utilized by the study staff will be password- and virus-protected with regular software updates and periodic mandatory changes of passwords. Any tablet devices utilized the study team will be encrypted by FRI information technology staff. In the event of data transfers, secure file transfers will only be performed between FRI server-maintained computers to NKI server-maintained computers (both accessible by each MPI). All study-related data will be edited, cleaned, de-identified and analyzed as needed for the preparing of conference abstracts and manuscripts.

Potential risks to participants

Participants across all components of this research project will experience minimal attendant risk. The intervention being proposed, including the use of text messaging and feedback of risk of negative treatment outcomes to the patient themselves imposes minimal risk above the patient's existing efforts to enroll in telemedicine-based opioid treatment. However, since the study involves the enrollment of PWUO, we will further minimize potential risks in the study by: 1) having all study staff conducting study procedures to undergo the Collaborative Institutional Training Initiative (CITI) program prior to performing any study activities; 2) receive a federal Certificate of Confidentiality to minimize any social and/or legal risks associated with inadvertent disclosure to others of one's same sex behavior, drug use and any other potentially stigmatizing statuses; and 3) providing NYC Department of Health pamphlets offering information on accessible harm reduction, OUD treatment, primary care, and social services to avert threats to voluntariness in which potential participants may feel obligated to join the study since they lack access to available services.

Risk of loss of confidentiality: As private identifiable information will be collected as part of study procedures, the risk of loss of confidentiality is recognized for all participants. OUD patients additionally may face the inconvenience of repeated study visits and engagement with the peer recovery coach. Protections against this risk are described in 2b.

Risks of distress associated with text messaging: This project centers on a text messaging system that supports PWUO participants to engage with opioid use disorder and social services. Although our prior feasibility studies have not yielded *any* adverse events related to the use of text messaging, the clinical application of any mobile health intervention comes with the attendant risks of imperfect understanding and use of this information. However, to mitigate this risk, the proposed multimodal texting intervention has undergone extensive refinement and to date, has not elicited any episodes of emotional distress. In the event PWUO participants find that the intervention is intrusive, eliciting emotional distress, or any other adverse events, they can simply reply *Stop* to the texting software and/or notify study staff to discontinue their continued receipt of passive reminders and informational texts. Protections against this risk are described further in 2b. In addition, during enrollment, PWUO participants in Aim 1 will be given verbal and printed instructions by the study staff to exclude the use of any identifiers during text communication, to regularly delete text messages exchanged with study staff and the HIPAA-compliant server, password protect their mobile phones and periodically change phone passwords, avoid sharing their mobile phone with friends or family, immediately report any breach of privacy committed by peers, avoid granting mobile app permissions, remain vigilant when downloading files or clicking hyperlinks from suspicious texts or emails on their phone, considering mobile phone device protection with security software that ensure personal firewalls, spam filters, anti-virus and anti-spyware tools, encrypt all data stored on their phone (e.g., for Android phones version 4.0 or greater, iOS running version 4.0 or higher) using federally verified encryption applications that offer a passcode to automatically encrypt all data, and avoid using open Wi-Fi.

Risks of distress associated with text message contact with PRCs: The efficacious CSH training developed by Drs. Lewis and Lekas has reliably trained PRCs to mitigate any conflicts of interest, bias, stigma, or role conflict by emphasizing the following training topics: 1) reducing stigma (internalized, anticipated, and experienced) among PWUO; 2) generating cultural and structural humility and self-reflection; 3) strengthening PRC-participant rapport and communication; and 4) establishing meaningful boundaries between PRC and participants to mitigate role conflict. Their prior studies have not elicited any adverse events related to PRC support for study participants.

Adequacy of Protection Against Risks

Informed Consent and Assent will be accomplished by ensuring that all PWUOs will be consented by trained research staff, with research training approved by the IRB (see **Single IRB Plan**). If PWUOs indicate willingness to be contacted by research staff, they will complete verbal consent by trained study staff. If requested, PWUOs will be given paper copies to read the informed consent document and/or review the document with staff, and a HIPAA review will be provided during their baseline enrollment. The risks of study participation will be clearly defined for all participants. Consent will be obtained via REDCap, and we will request from the IRB and obtain a waiver of signed consent. HIPAA will be signed using secure IRB-approved signing software. Throughout the consent process, the study staff member will be assessing consent capacity and if the individual is deemed to have the capacity to consent, they will be enrolled once consent and HIPAA procedures are completed. For Aim 2, informed consent (for all 3 stakeholder groups) and HIPAA (for the PWUO participants) procedures will be completed via video (Zoom or WebEx).

Protections Against Risk and Risk of loss of confidentiality. Our team has decades of research experience working with underserved community-enrolled people who use opioids. We recognize that some participants may feel uncomfortable when answering certain questions, especially PWUO participants. Specifically, discussions about drug use and other risk behavior, and about their experiences with the healthcare system, including OUD services may be distressing. Description of prior overdose and incarceration experiences may also cause some psychological discomfort or distress. Participants may choose to skip these questions. Additional social services referrals will be provided and transportation fare for immediate specialty care consults. All study staff will be trained in the provision of immediate referrals to primary care and social services.

As a guard against the loss of confidentiality, all information will be stored in locked password-protected files which will be accessible only to members of the research staff for this project and stored on secure filesystems. No names or other identifying information will be used in publications, which will stem from this research. All data collected (including results of tasks, tests and questionnaires) will be identified with a unique subject-specific code and will be kept in password-protected electronic files that will be stored in a secure drive designated for this study. Survey data, and audio files will be assigned an identification code and collected on password-protected, encrypted tablets. Survey data will then be downloaded to a password-protected desktop at the respective collaboration sites and stored on their HIPAA drive. Participant personal identifying information will be kept separately from survey and the audio files/transcript data and identification codes will not be linked to participant's personal information. Participant information will be destroyed once data collection is complete and all participants have received their compensation. All records will be kept for at least 3 years after the end of the study. After this retention period expires and the study is closed, all records will be electronically scanned and any paper records will be thereafter shredded or otherwise destroyed. Great care will be taken to comply with The Confidentiality of Alcohol and Drug Abuse Patient Records Regulation under the Code of Federal Regulations 45 CFR Part 2 and the HIPAA Privacy Rule: Programs may not use or disclose any information about any patient unless the patient has consented in writing (on a form that meets the requirements established by the regulations) or unless another very limited exception specified in the regulations applies. Any disclosure must be limited to the information necessary to carry out the purpose of the disclosure. The Privacy Rule permits uses and disclosures for “treatment, payment and health care operations” as well as certain other disclosures without the individual’s prior written authorization. Disclosures not otherwise specifically permitted or required by the Privacy Rule must have an authorization that meets

certain requirements. With certain exceptions, the Privacy Rule generally requires that uses and disclosures of PHI be the minimum necessary for the intended purpose of the use or disclosure (Health & Services, 2004).

For the PWUO survey participants, consent and data collection taking place will be either over the phone or in a quiet and private location in the listed study offices where, if necessary, noise machines will also be used. For the in-depth interviews with key stakeholders in Aim 2, the HIPAA compliant version of Zoom and Webex platforms will be utilized.

During Aim 2, we will also obtain a signed HIPAA authorization from participants to audit the EPIC EHR "Care Everywhere" feature to capture health systems utilization in the study site hospital and elsewhere. Drs. Lekas and Lewis will lead the data collection and analysis of the implementation data including triangulation of the qualitative interview data with the EHR data and other process data to evaluate the adoption, implementation, and maintenance of the intervention.

Due to the remote nature of this study, additional precautions have been taken to ensure protection against loss of confidentiality in the transmission or storage of mHealth data. The proposed texting intervention we propose to employ for data capture is built on a standard HIPAA-compliant platform by QliqSOFT, which employs encryption protocols defined for use in the United States National Institute of Standards and Technology (NIST) publication FIPS 140-2, or any superseding documents according to the date of implementation. The use of the Advanced Encryption Standard (AES) allows for symmetric encryption and is certified as HIPAA compliant.

QliqSOFT's platform includes a chatbot feature that enables secure communication. This chatbot will use patient identifiers, such as names, to personalize the user experience. It's important to note that the chatbot requires participants to have a data plan, as it operates through a hyperlink rather than standard SMS. This ensures a secure and seamless interaction experience, further enhancing the confidentiality and security of the communication.

Incidental Findings: Participants will not complete medical imaging or pregnancy testing as a component of study procedures, so we do not anticipate these incidental findings. During Aim 1, patient participants will have access to study staff during regular work hours where they may incidentally report imminent threats to themselves or others. Incidental findings of imminent threat will be handled in the same way as in in-person research, as reviewed by our sIRB. Specifically, incidental findings will be escalated to Dr. Babak Tofighi (MPI) who will determine appropriate follow-up based on the perceived level of threat. All SAEs will be logged and reviewed as explained elsewhere in this application.

Vulnerable Subjects. Participants with a history of criminal justice involvement will be eligible for recruitment into this study. Their capacity to consent is not considered to be different from the rest of the participants in this study; therefore, capacity to consent will be assessed with the same consent comprehension tool as other participants. Individuals from age 18-21 may be consented into this study as they may be interested in engaging engaged in treatment for OUD, but children under the age of 18 will not be eligible for participation.

Participants with a history of OUD will be approached by study staff to assess for eligibility in the study. Since nearly all potential participants will be experiencing socio-economic and health-related challenges (e.g., lack of housing, unemployment, healthcare access), we will minimize potential ethical challenges and risks in the study by: 1) training study staff in the ethical conduct of research with populations experiencing substance use disorders, led by Dr. Tofighi, who presents the same topic to medical students, trainees, and research staff; 2) training study staff in coordinating receipt of federal Certificates of Confidentiality for participants to minimize any social and/or legal risks associated with inadvertent disclosure to others of one's same sex behavior, drug use and any other potentially stigmatizing statuses; 3) providing NYC Department

of Health pamphlets offering information on accessible harm reduction and treatment services for all individuals approached by study staff to avert threats to voluntariness in which potential participants may feel obligated to join the study since they lack information or access to treatment options; 4) to overcome additional challenges with voluntariness, potential PWUO participants will also be given city government pamphlets clarifying how to access social services that address social determinants of health, since PWUO may be in dire social, financial and health circumstances that would make them feel obligated to join a research study to receive financial reimbursements and potential support linking with treatment and social services; and 5) given the severity of OUD and its impact on reducing access to healthcare, individuals may be experiencing undiagnosed, unmanaged, and/or undermanaged medical and/or psychiatric conditions, and will be provided with informational pamphlets published by the NYC Department of Health on free healthcare services tailored to low-income and vulnerable PWUO. In addition, potential PWUO participants will be informed by the study team using written pamphlets that publicly listed primary care clinics in proximity to the patient's location may facilitate referrals to psychiatric and specialty care services to ensure optimal and personalized care.

Potential Benefits of the Proposed Research to Research Participants and Others. There are no direct clinical benefits for participating in this study, for PWUOs, providers, or caregivers. However, participants may find engagement with our texting intervention and/or text contact with the peer recovery coach satisfying, as has been observed in our prior pilot studies. Thus, the relation of minimal benefits to minimal risk of loss of confidentiality (which is greatly attenuated by our extensive privacy and security systems) is commensurate with other basic behavioral research.

Importance of Knowledge to be Gained. The unifying goal of all Aims of this proposal is to develop a multimodal intervention that leverages text messaging to support patient engagement with OUD- and social services, based on the mechanisms underlying treatment outcomes. If successful, this suite of studies would contribute not only to the basic understanding of factors influencing engagement with treatment among underserved Black and Latinx PWUOs, but also would set the stage for a potential future effectiveness-implementation hybrid type 1 trial, at low cost and with key stakeholder support. In the context of rising rates of OUD and opioid overdose among underserved Black and Latinx PWUOs, the development of such a tool provides a substantial contribution not only to science, but also to human health that aligns with federal guidelines to reduce health inequities among PWUO. Thus, the substantial benefits of the knowledge to be gained outweigh the minimal risk of loss of confidentiality (attenuated as above).

Data-safety and Monitoring Plan

The IRB's Principal Investigator (Tofighi; MPI) will be responsible for monitoring the safety and efficacy of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. The IRB's PI will provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of AEs and SAEs, and any actions or changes with respect to the protocol.

Data Monitoring Plan

As a guard against the loss of confidentiality, all patient participant survey instrument responses will be stored in REDCap, which is an encrypted password-protected platform that will be accessible only to members of the research staff for this project and stored on secure filesystems. No names or other identifying information will be used in publications, which will stem from this research. All records will be kept for at least 3 years after the end of the study. After this retention period expires and the study is closed, all paper records will be electronically scanned, and any paper records will be thereafter shredded or otherwise destroyed. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Further information about data transmission is presented in our **Protection of Human Subjects** document, under "Protections Against Risk", and is depicted in **Supplemental Figure 1.** The platform we propose to employ for the texting intervention is built on a standard HIPAA-compliant cloud, and the entire end-to-end solution has been certified as HIPAA compliant. Complete details can be found in the Protection of Human Subjects section. This HIPAA-compliant system maintains fully auditable data access logs that are required for any HIPAA system.

Data Entry & Analysis

Data analysis will be automated as much as possible. As there is negligible transcription of data, errors in data entry introduced by experimental staff should be minimal. When data must be entered by hand (for example during focus group sessions), data will be double-entered and checked for accuracy using standard data shells.

In **Aim 1,** all participants will be assigned a survey ID accompanied by their phone number and name. This master-list survey database will be stored in a password protected FRI server. Participant data will be stored in REDCap and will be accessible only to members of the research staff. Data analysis will be automated as much as possible. As there is negligible transcription of data, errors in data entry introduced by experimental staff should be minimal. When data must be entered by hand (for example during focus group sessions), data will be double-entered and checked for accuracy using standard data shells. Our proposed analysis will use all available data, under an intent-to-treat principle. As a first step, we will generate descriptive statistics to characterize the sample at baseline on sociodemographic, health and psychiatric symptoms, substance use, and technology use characteristics, both overall and by intervention group (texting + PRC vs. texting only vs. TAU). Descriptive statistics include means, standard deviations, percentiles, and frequencies with percentages, as appropriate. Then, in support of Aim 1, we will investigate the impact of the three-arm intervention on primary outcomes. To assess these hypotheses (see **Data Analysis, Aim 1**), we will utilize the Cox regression model to investigate whether there are differences in time to service linkage (in weeks) by intervention group. Cox regression is a method for investigating the effect of several variables upon the time to a specified event. Data collected at 3-, 6-, and 12-month follow-up surveys as well as from the participant

EHR will permit analysis of secondary outcomes of engagement in intervention and durability of treatment effect. For these analyses, we will use logistic regression to model binary outcomes indicating longitudinal engagement in 26-week treatment (yes/no) and continuous retention in primary care-based buprenorphine treatment at 3-, 6-, and 12-months (yes/no) with no more than a 28-day gap in receiving an active buprenorphine prescription over each period. To assess whether randomization was successful, we will compare the distribution of demographic characteristics, PhenX consensus measures, medical/psychiatric history, and technology use patterns (see Data Collection) by intervention arm. Variables contributing to baseline imbalance will be included as model adjustment variables. To ensure that model assumption of non-informative censoring/study drop out is reasonable and avoid potential bias, we will compare dropout rates between intervention groups as well as other measured variables, e.g., demographic, social determinants, and risk behavior variables. If there is empirical evidence of nonrandom dropout, we will model the dropout event using available factors to identify and estimate their influence.

In **Aim 2**, interview transcripts will be content analyzed by the study team by utilizing a 7-step process refined by our team following numerous NIDA-funded studies. This process allows for a systematic identification of subcode, codes and themes while keeping the data contextualized. The process is comprised of the following stages: In step 1, we will identify the principal issues discussed by participants. During step 2, we will construct preliminary definitions of the analytic themes. In step 3, we will Develop and apply core codes and subcodes to the initial set of interviews. Blocks of text within text tagged with core codes will be assigned subcodes. In step 4, we will develop a provisional coding scheme. In step 5, we will test the provisional coding scheme by coding new transcripts. During step 6, we will reconcile coding differences and construct a final coding scheme. Lastly, during step 7, we will apply the coding scheme to the full dataset. Close reading of the coded interview transcripts will reveal data patterns withing each sample, but importantly, highlight differences/similarities across the stakeholder groups, key to intervention adoption implementation and maintenance. For instance, an emerging data pattern in the frontline provider interviews could be that they strongly recommend changes in policies and guidelines that will afford them with flexibility in enrollment and referrals to better engage PWUO in care, whereas the PWUO might emphasize the role of OUD intersecting stigma in undermining their engagement in care and highlight how interactive texting from PRCs reduces internalized stigma and increases intervention adoption. This prismatic assessment of the intervention will enable us to draw inferences that will inform the refinement of the intervention for a future scale up project.

In **Aim 3,** the economic evaluation will be conducted using well-established guidelines of prospective economic evaluations alongside clinical trials. Outcome measures will be analyzed using multivariable generalized-linear mixed models (GLMMs) to adjust for potential confounding factors and the skewed distributions commonly associated with healthcare cost data and censored outcomes (e.g., QALY). The GLMM, an extension of the GLM, allows the most appropriate mean and variance functions to be chosen based on the observed data, as well as for the inclusion of random effects. The primary outcomes for Aim 3a will be the budget impact tool consolidating the resources and associated costs required to implement and sustain the PRC-supported text contact + interactive text messaging, and interactive text messaging only interventions compared to TAU. The primary outcome of Aim 3b will be **the incremental cost-effectiveness ratio** (ICER), defined here as the incremental mean cost between the two intervention arms and TAU divided by the incremental mean effectiveness of the two arms calculated separately. HRQoL is increasingly recognized as a key indicator of patient well-being that is not captured in clinical measures. The QALY is a measure that combines the HRQoL associated with an individual's health state and their time spent in that state. The QALY is

recommended as the primary effectiveness measure in economic evaluations due to its ability to be compared across interventions and disorders, and its association with commonly accepted value thresholds (i.e., cost-per-QALY). OUD treatment days is an important continuous measure of effectiveness for clinical stakeholders and calculating cost-per-OUD treatment days enables comparisons with existing economic evaluations of other inpatient interventions reporting similar clinical effectiveness measures. As part of the process of estimating ICERS we will be able to test the 6- and 12-month post-intervention differences between arms of a) the average total costs to the healthcare sector, state policymaker, and society by resource categories; and b) the average QALYs and OUD treatment days; thus, two ICERs will be calculated for each of the three stakeholder perspective for each of the aforementioned evaluation periods.

Safety Monitoring Plan

During screening in Aims 1 and 2, potential study participants will be approached by study staff to determine their eligibility for their participation in this study. Information about their substance use history, current pharmacological treatment, history of prior treatment or illicit opioid reuse, along with other relevant clinical information, will, with the participant's consent, be asked of them during baseline enrollment.

Data pertaining to patient participant entry into primary care-based buprenorphine treatment will include EHR appointment records, dispensing records, completion of specialty care referrals, and appointment adherence data that will be audited from their clinical chart by the research staff.

A **social harm monitoring plan** will be utilized during scheduled study visits to query for any potential social harms due to study enrollment. Inherent in research among PWUO is the potential for physical, emotional, and psychosocial harm to study participants that are non-medical adverse experiences. *Case Report Forms* will systematically capture social harm in a two-tiered manner by asking participants whether they "experienced any problems since the last study visit as a result of being enrolled in the study or receiving text messages from the study?" If respondents confirm social harm, they will be asked in more detail regarding categories of experienced harms, including emotional, physical, economic, and/or "other" harms. Each social harm incident will be characterized as being related to peers, friends/family, partner(s), employers, and/or healthcare and social service providers. Participants will then be asked to specify the adverse social incidences, including stigma, discrimination, and/or difficulties in personal relationships following study enrollment and receipt of text message content. Lastly, study staff will query respondents regarding the frequency of past week distress symptoms and resolution status (Yes/No). Any social harm events will be communicated to Drs. Tofighi and Lekas (MPIs) within 24 hours and will coordinate with trained PRC staff to provide multichannel support to promptly address events using information-based approaches (e.g., informational pamphlets) and skills-building approaches (e.g., in-person or audio/visit sessions with PRCs). This multi-intervention approach is based on prior study findings describing the need to maximize responses that can ensure optimal support and potentially synergistic benefits among PWUO and persons living with HIV enrolling in clinical trials.

Quality Assurance Plan

We realize that there is potential for a participant to enroll in the study more than once if protections are not put in place to prevent, or at least minimize, this occurrence. To begin with, all participants will be asked for identification and in the event that a participant does not have ID, other items that include name and birth date such as the Benefits ID card, medical documents, birth certificate, voter registration, court papers, etc. will be accepted if accompanied by a picture ID that shows the participant's name and photo (student ID, employment ID, etc.). In addition, personal identifying information such as birth date and

mother's maiden name will be collected at enrollment and research staff will log this information into a password protected database that will be updated into a master list of participants enrolled every day. Prior to enrollment, participants' names will be checked in this master database. While these efforts may not fully protect against duplicate enrollment, we feel it will greatly minimize this occurrence and potential bias.

Approximately 5% of sessions from each intervention arm will be randomly selected to be audio-recorded. Participants will sign a separate consent form to agree to this recording. If a participant declines, the next randomly selected individual will be recorded. To ensure the quality and integrity of the randomization, it is important to minimize contamination across conditions. Therefore, we will (1) schedule in-person study visits in a private room or space to ensure conversations are not overheard; (2) reduce the potential for overlap of participants assigned to different arms by scheduling only one study arm on a particular day; and (3) assess potential contamination by asking participants if they heard about the study prior to entry, if they know anyone who has participated in the study and compare these instances by study arm. Our past work indicates that contamination is unlikely. However, if a participant reports knowing others in the study, they will be asked to share the individual's name so that a variable can be created that indicates potential contamination which will be considered in the analysis.

Collection and Reporting of SAEs and AEs

Patient Cohort. In this study we will use the FDA definition of serious adverse events (SAEs). Both adverse events (AEs) and SAEs will be systematically assessed at each clinic visit for the patient-participants. We do not anticipate SAEs are AEs related to the use of text messaging which is our intervention. Any SAE, whether or not related to study intervention, will be reported to the IRB and NIDA. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will be monitored by the investigator via ongoing status assessment until 1) a resolution is reached, for example the problem requiring hospitalization has resolved or stabilized with no further changes expected, 2) the SAE is determined to be clearly unrelated to the study intervention, or 3) the SAE results in death. SAEs would include hospitalization (for example as the result of an opioid overdose, which is not uncommon among high-risk OUD patients) or opiate overdose resulting in death. The study team will conduct, at a minimum, an annual Data Safety Board meeting to review all SAEs. All PI's will attend this meeting. If more than 2 SAEs occur in any year, meetings of the board will be increased in frequency. All observed SAEs (again, regardless of relation to the study intervention) will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA. The MPIs will be responsible for monitoring and recording both AEs and SAEs.

Provider and administrator study participants providing in-depth interview data. We do not anticipate any AEs or SAEs for the clinician and administrator participants undergoing virtual in-depth interviews (Aim 2). For this sample we will also adopt the FDA definition of an SAE. AEs and SAEs for the provider and administrator sample will be handled exactly as specified for the PWUO participant cohort.

Standard AE definitions will include the following:

> **Adverse event:** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding),

symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research*. For the purposes of this study, we will not monitor known reactions to methadone or buprenorphine treatment as adverse reactions. These known reactions are specified on the FDA-approved package inserts for the medications used in this study.* These include dizziness, drowsiness, withdrawal symptoms, tongue pain, nausea, vomiting, constipation, headache, insomnia, and trouble concentrating.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/ birth defect
- Based on the appropriate medical judgement, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

AEs are graded according to the following scale:

Mild: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

Appropriately qualified and trained study personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events assessment and collection will begin when the participant signs the informed consent form and follow-up will continue through 30 days after the last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

All AEs and SAEs are reported to the WCG IRB according to their reporting guidelines.
Standard reporting, within 7 calendar days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site staff's

knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

Reporting mechanisms of IRB actions to NIDA
Any IRB action that impacts study protocol or that has no impact on study protocol will be reported to NIDA program official within 24 hours of notification from IRB. This will be done via email and followed up with official documentation. Any changes to study protocol that is not an IRB action, but a sole decision of the PI will also be communicated to NIDA program *prior* to the implementation of the change.

Plan for Incidental Findings Management
If an incidental finding is discovered during screening procedures, the participant will be notified and given a proper referral to a service provider. Moreover, Dr. Tofighi will draft and approve the training of study staff protocols for the referrals to OUD treatment and primary care services. In case of an adverse event as a result of study participation, the contact PI will be responsible for reporting to the IRB of record.

Conflict of interest
Any conflicts of interest will be reported to the IRB.

Responsibility for data and safety monitoring
The MPIs (Lekas, Lewis and Tofighi) will be responsible for monitoring the study.

Frequency of DSM reviews
As indicated above, on a monthly basis, the MPI will meet with the study team to review notes and assess issues of community concern about potential disclosure issues or reports of adverse consequences.

Content of DSM report
The following will be included in the DSM report: 1) brief description of protocol, 2) baseline socio-demographic characteristics, 3) retention and disposition of study participants, 4) quality assurance issues, 5) AEs, 6) SAEs, 7) efficacy, 8) suggested and actual protocol changes

Interim Data Analysis Plans

Interim analyses will be performed to evaluate safety. At each DSMB meeting, all SAEs will be evaluated and compared between study groups. If SAEs differ between groups in a manner determined to be related to study procedures, the study will be paused. Decisions to pause the study will be made by the independent DSMB.

In addition to consistent monitoring by members of the research team for adverse events, quarterly interim analyses of the survey data, quality control checks, and study activities will also be performed to ensure that all participant data are protected and there are no adverse events or harm to participants. During this review, validity and integrity of the data will also be monitored.

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