1) Protocol Title

Piloting a naloxone intervention in an emergency response community to reduce opioid overdoses in Philadelphia

2) IRB Review History

Does not apply

3) Objectives

We propose a study to develop and pilot test a pragmatic community intervention enabling rapid naloxone delivery by stakeholders including non-medical opioid users (NMOU) – persons misusing prescription opioids/heroin - and good Samaritan community members (CM) during overdose emergencies. Opioid-related overdose is a major public health problem and a leading cause of mortality.[1–4] The timely use of naloxone in opioid overdose situations can be crucial.[5] Health policy, legislation, and research funding have converged in support of community-based opioid Overdose Prevention Programs (OPP) that distribute naloxone, an opioid antagonist.[6–8] We observe three apparent tendencies in populations commonly studied for overdose behavior: (a) delays or a reluctance to call Emergency Medical Services/911 – even in light of the legislative changes of recent years; (b) a willingness amongst bystanders and victims to seek and/or administer naloxone in an overdose situation; and (c) the growing use of OPPs to both distribute naloxone and conduct support group sessions. A recent study[9] reports that injection drug users participating in OPP express significant concerns with attracting police, with the victim calling 911 in only 23% of overdose events. Findings of drug user studies consistently connect the reluctance or delay in calling and involving 911/EMS with the critical time-response factor.[10] The documented existence of the 'buddy ethic' between drug users who 'watch out for each other' when using drugs presents a behavioral model that can be leveraged for broader pro-social intervention.[11] This proposed new intervention leverages the growing success of naloxone distribution programs and will empower NMOU communities to provide rapid, secure, and effective emergency response to support each other in the event of overdose. This intervention is designed to augment EMS by potentially delivering naloxone to overdose victims more rapidly using a smartphone application (app). Emergency Response Communities (ERC) are specialized smartphone-based social networks in which members are approved carriers and/or potential users of a specific medication or treatment.[12] The ERC approach is ideally suited to support, facilitate, and encourage naloxone administration in opioid overdose emergencies. ERC uses a shared-condition membership model in which available members in possession of a life-preserving medication and smartphone are alerted to respond to emergency requests made by other members. This model combines GPS and IP-location tracking plus an underlying information system to automatically identify potential responding members, simulates a pharmaco-spatial response area around a person in need, and guides those agreeing to respond to the intervention target. ERC effectiveness is predicated on the observation that while most community members will not comply and carry their prescribed medication (naloxone) at all times, within a given population at any one time, there will be a sufficient number of compliant individual members to elicit a positive response within minutes.[12,13] ERCs can increase event driven access to naloxone in overdose situations, which may have a significant public health impact. Towards this end, we

are proposing to utilize an ERC in the development and pilot testing of a smartphone app-based naxolone intervention (ERC-NAX). Research is required to understand the needs and barriers in NMOU communities that will enable effective design, adaption, and implementation of the proposed ERC-NAX app.

Aim 1: Identify barriers and facilitators of acceptance and use of a smartphone-based ERC naloxone intervention program. Finalize the initial ERC-NAX app design based on stakeholder inputs for key features and functionality; and implement the app prototype.

Aim 2: Pilot test the implementation of ERC-NAX in an ERC consisting of 55 non-medical opioid users and 55 community members. Develop and apply metrics that: measure perceived usability and usefulness; online and physical proximity/availability; alert and response behaviors; and drug use and overdose risk behaviors.

Aim 3: Synthesize the knowledge acquired in Aims 1 and 2 to (a) revise the pilot app design and specifications; (b) determine which metrics were useful and effectively collected; (c) confirm efficacy of recruitment procedures, retention/adherence, and assessment procedures; and (d) develop a field study implementation manual; all of which will be used in a subsequent study to conduct a large-scale, multi-site implementation trial.

This 3-year study will provide us with actionable evidence regarding the viability and acceptance of an app-based naloxone intervention following the ERC model. It will enable us to discover the barriers and motivators for app use amongst community members, and fine-tune NMOU and other stakeholder requirements. To achieve Aim 1, we will modify and validate our current ERC design by conducting qualitative interviews and focus groups with stakeholders, which will be followed by rapid development of the app. In Aim 2, we will pilot the ERC-NAX app in partnership with an OPP in a geographically defined urban area of Philadelphia by distributing the app to a test population of NMOU and community support members and providing initial training and technical assistance. This will lead us towards with the goal of assessing the acceptability and effective use of the app by stakeholders. In Aim 3, we will prepare the groundwork for a study across larger populations enabling us to measure the endpoint impacts of the intervention, which include the potential positive effect on adherence levels (naloxone carrying); and provision of naloxone in overdose emergencies.

4) Background

SIGNIFICANCE

Fatal and non-fatal opioid overdose is a significant national public health problem. The U.S. is amidst an escalating drug overdose epidemic. In 2014, 47,055 people died from drug overdose in the United States that exceeds the number of overdose deaths in any other previous year on record.[4] From 2000 to 2014, the age-adjusted rates of overdose deaths have risen 137%, from 6.2 per 100,000 in 2000 to 14.7 per 100,000 in 2014.[4] In 2014, drug overdose deaths in the United States outnumbered deaths from motor vehicle crashes by approximately one and a half times.4 Illicit and prescription opioids, including heroin and opioid pain relievers, have contributed to the majority (61%) of drug overdoses in 2014.[4] From 2000 to 2014, death rates from overdoses involving any opioid has increased 200%.4 The societal burden of opioid-related premature

mortality is substantial: opioid-related deaths accounted for an estimated 500,000 potential years of life lost each year[14]; more than $18 billion future earnings were estimated to be lost due to overdose in 2009.[15] Non-fatal overdose is also a significant burden for public health infrastructure; in the United States, an estimated 1.1 million emergency department visits were made each year for drug poisoning during 2008-11.[16]

Fatal and non-fatal opioid overdose is a significant public health problem in Philadelphia. Death due to drug overdose is a significant and rising cause of mortality and morbidity in Philadelphia. In 2015, almost 700 drug overdose deaths were reported in Philadelphia – twice as many as deaths from homicide.[17] Public health officials are predicting that overdose deaths in 2016 are likely to reach 900.[18] On one day in November 2016, 50 overdoses were reported (5 fatal).[18] In December 2016, an unprecedented 35 fatal overdoses occurred in a 36 hour period.[18] Heroin and prescription opioids are key drugs involved in overdose[19] and readily available on the local black market.[20] Importantly, Philadelphia is located along a primary drug trafficking corridor that has historically offered the purest and cheapest heroin on the East Coast.[20] During 2009-2014, 43% increase in drug overdose deaths in Philadelphia was accompanied by 45% increase in overdose deaths related to heroin.[21] A recent outbreak in overdose deaths has been linked to the non-medical use of fentanyl, a prescription opioid 50 to 100 times as potent as morphine[22]; fentanyl-related deaths have risen more than 600% between 2013 and 2015.[23] In Philadelphia, for each opioid-related death, there were 12 emergency department visits for opioid overdose in 2015.[17] The share of ED visits for opioid overdoses among all ED visits has grown from 0.4% in 2007 to 0.7% in 2015.[17]

Naloxone is increasingly available as a tool to combat opioid overdoses in Philadelphia. In November 2014, Pennsylvania passed Act 139, a state's version of Good Samaritan Law.[24] Prior to Act 139, only paramedics and intermediate level emergency medical technicians were authorized to administer naloxone.[25] The law expanded access to naloxone for law enforcement officers and firefighters. Act 139 also allowed medical professionals to prescribe, dispense, and distribute naloxone – directly or through a standing order - to laypersons, including persons at risk of opioid-related overdose, family members, friends, or other persons with close contact to those at risk for opioid overdose. Pursuant to Act 139, in 2015, Pennsylvania's Physician General signed a standing order prescription for naloxone, available as Standing Order DOH-002-2015,[26] and later Standing Order DOH-002-2016.[27] The standing order allows any person to request intranasal naloxone or intramuscular naloxone administered by auto-injector at a pharmacy that carries this medication.

Bystanders are willing to respond to drug overdoses. There is emerging literature on willingness and effectiveness of bystanders to respond to an overdose event and administer naloxone. A 2015 review of data from four studies found bystander naloxone administration to be associated with increased odds of recovery for overdose victims.[10] Walley et al. (2016) found that among community responders trained in overdose prevention and naloxone administration, help-seeking (calling 911 and/or EMS present) increased over time and was more likely when response to naloxone took longer or naloxone didn't work.[28] Bagley et al. (2015) demonstrated that family members of drug users have high motivation for uptake of overdose trainings and they will use naloxone in case of overdose emergency.[29]

Ecological Momentary Assessments, effective in gathering real-time data on drug users, set the stage for Ecological Momentary Interventions to deliver just-in-time emergency health response for overdose. By 2015, 64% of Americans owned a smartphone.[30] Innovations in the application of technology to areas of smartphone users' lives have led to the rise of mobile health (mHealth) technology, which is increasingly being used to deliver public health interventions.[31] A promising methodology is the use of ecological momentary assessment (EMA) to capture multiple observations of a user's health behavior.[32] EMA allows researchers to receive regular reports from research participants on behaviors or experiences close to real time, leading to improved accuracy in measurement and decreasing recall bias.[33] EMA methods have been successfully applied to different populations, including people with mental or physical illness and people who use drugs.[34,35] EMA can be used to explore contextual factors related to drug use such as location of use, triggers and factors influencing variations in patterns of use.[32,33] Preliminary applications of EMA with people who inject drugs are promising,[36,37] however, there is an even greater need to shift from assessment to intervention, in the form of Ecological Momentary Interventions (EMI). EMI has yet to be studied to understand the context of opioid overdose and response.

EMI are typically designed with a focus on individuals by using their personal smartphone to deliver tailored health interventions. EMI is being used by our team in the study of epinephrine delivery in anaphylaxis events.[12,38] The proposed study builds on our successful use of EMI at the individual level, and connects smartphone users to one another to build a network that collectively supports health intervention. Smartphones are increasingly being utilized for innovative approaches to support emergency response because their sensors can be used to transmit the user's location and other critical information.[39,40] The use of smartphone systems that connect users and collectively mobilize them to respond to a critical health event has been a new development across the world in recent years,[41-43] but research in this area is in its infancy. Research is needed to provide evidence for feasibility, appropriate design, and dissemination, and to measure impact on response efforts and health outcomes.

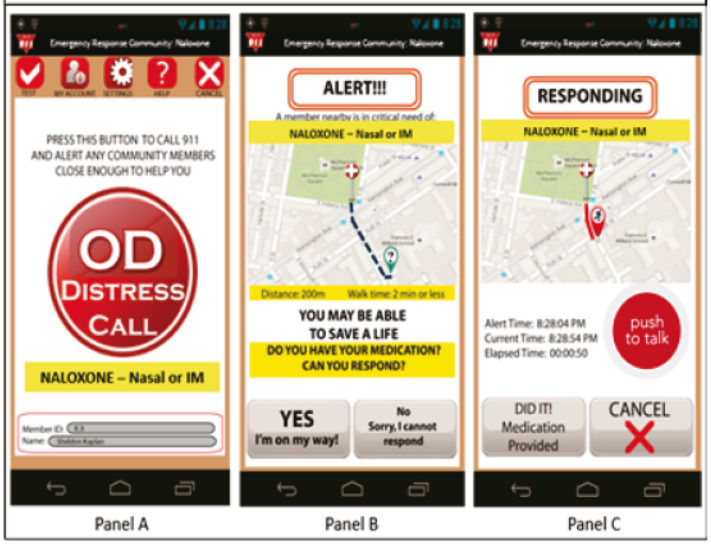
The Food and Drug Administration (FDA) launched a Naloxone App Competition in 2016. To highlight the significance and demand for the proposed mobile phone app, the FDA recently announced a competition towards the "development of a low-cost, scalable, crowd-sourced mobile phone application that helps increase the likelihood that opioid users, their immediate personal networks, and first responders are able to identify and react to an overdose by administering naloxone."[44] The winning application will receive $40,000 to help in the development of the naloxone application. The FDA announcement was released after we began developing the proposed application in early 2016. While we are encouraged by the FDA announcement, we believe an interdisciplinary, community-engaged, evidence-based approach is needed to develop a successful and scalable naloxone app.

INNOVATION

A new class of Ecological Momentary Intervention (EMI) will be piloted to reduce overdose in a high risk population. mHealth apps have ushered in a new age of participatory medicine and led to a sharp increase in the availability of apps supporting medically motivated real-world

interaction between users, leading to potentially significant changes in healthcare delivery.[45] Smartphone applications, which can support the connection of app users to real-world medical emergency events, are being studied in diverse situations such as the mapping and response-use of Automatic Electronic Defibrillators,[46-50] volunteer emergency response,[51-55] physical proximity of diabetes patients[56] in need of glucose or monitors, and allergy community support for anaphylaxis events.[12,38] We have the potential to enable emergency response in which the social network-based connection between individuals creates a lay-layer of support which can augment EMS. Applying this approach to the emergency provision of naloxone for overdose has never been attempted. Recent developments such as the PA Standing Order for naloxone, supportive good Samaritan laws, increased smartphone adoption, and the maturity of mobile tracking/alert technologies all support this innovative intervention. The potential for positive impact by increasing overdose reversal rates is immense.

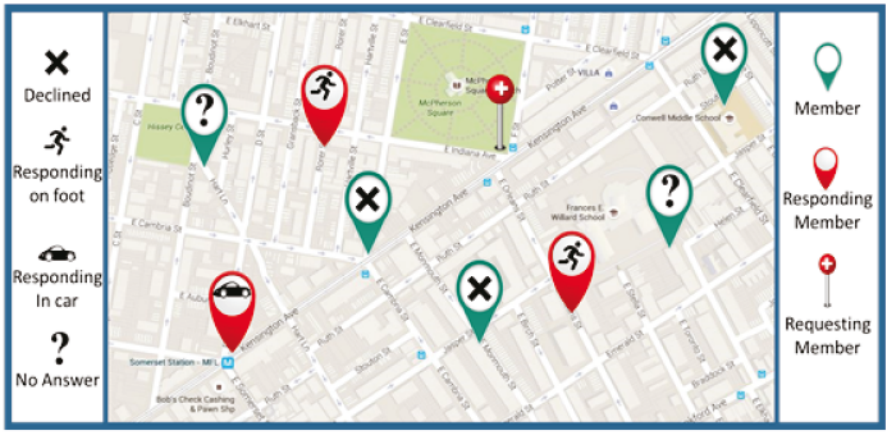
Figure 1: Example of ERC-Nax Interface Design



Emergency Response Communities (ERC) will amplify the potential for naloxone to reverse opioid overdose by enabling immediate availability during an overdose event. ERC are social network-based EMIs in which members are approved carriers and/or potential users of a specific medication or treatment.[12]

Initially proposed to address anaphylaxis through the sharing of Adrenaline Auto-Injectors, the ERC approach is ideally suited to support, facilitate, and encourage naloxone use for overdose reversal. ERC uses a shared-condition membership model in which available members in possession of a life-preserving medication are alerted to respond to emergency requests made by other members (Figure 1). Members can be drug users, family members, bystanders, overdose prevention staff, or any potential stakeholder possessing both a prescription for naloxone and a willingness to respond in emergencies.

Figure 2: Pharmaco-spatial mapping of alert area in Kensington (Philadelphia)



This EMI utilizes GPS and IP-location tracking to identify potential responding members, modeling a pharmaco-spatial response area around a person in need (Figure 2), and guiding those agreeing to respond to the intervention target.

Opioid users can be empowered to help each other. ERC leverages known low adherence levels, predicated on the observation that while most community members will not comply and carry their prescribed medication at all times, within a given population at any one time there will be a sufficient number of compliant individual members to elicit a positive response within minutes – often faster than EMS/911 arrival times.[12,13,38] Preliminary research has resulted in the development of the ERC Effectiveness Model to assess the potential of condition-specific communities based on population density and prescription distribution characteristics.[13,57,58] Studies in shared identity and 'buddy behavior' show high levels of willingness to help.[59-61] These results support that responding to opioid overdose emergencies can be a highly effective intervention of an ERC.

A ERC-NAX app will be developed and tested in partnership with two community partners with extensive experience in overdose prevention – Prevention Point Philadelphia and Angels in Motion. Prevention Point Philadelphia (PPP), a multi-service harm reduction agency in the Kensington area of Philadelphia, began offer trainings in overdose prevention from 2006. Angels in Motion, a Philadelphia-based grassroots group of community members devoted to helping people suffering from drug addiction, was established in 2015 by parents of people who use drugs. Drawing upon the years of experience accrued by the members and clients of these two organizations will infuse a real-world utility to the design and development of the ERC-NAX app.

5) Inclusion and Exclusion Criteria

Inclusion criteria for NMOU and CM are found in Table 1. "Stakeholders" will be either NMOU or CM. NMOU will be active heroin/opioid users whereas CM will know active, former, or deceased NMOU. Both groups will live one of four zip code areas – adjacent sections in the eastern part of the Kensington section of Philadelphia – that encompass the residential areas with the highest drug overdose rates in city. Both groups will own a smartphone and maintain an ongoing cellphone data package. Participants will be asked to produce a smartphone, e.g., Apple, Android, and demonstrate competent use at enrollment. Participants who do not will be excluded. *Exclusion criteria* for both NMOU and CM include: live outside four zip codes in Table 1, younger than 18 years old, and does not speak/read English. For NMOU, an additional exclusion criteria is: did not use heroin or prescription opioid in the past 12 months. For CM, an additional exclusion criteria is: does not know active, former, or deceased NMOU.

Table 1 – Study Enrollment Criteria

Non-Medical Opioid Users (NMOU)	Community Members (CM)
1. Weekly misuse of heroin and/or rx opioid during past 30 days 2. Currently lives in zip codes 19122, 19125, 19133, 19134 3. 18 years old or older 4. Speaks/reads English.	1. Knows active, former, or deceased NMOU 2. Currently lives in zip codes 19122, 19125, 19133, 19134 3. 18 years old or older 4. Speaks/reads English.

No special vulnerable populations will be included in the study as indicated below:

- ☐ *Adults unable to consent*
- ☐ *Individuals who are not yet adults (infants, children, teenagers)*
- ☐ *Pregnant women*
- ☐ *Prisoners*
- ☒ *Not Applicable*

6) Study Timelines

The duration of an individual subject's participation in the study:

- Year 1: 10 stakeholders - participants of focus groups (1 hour), qualitative interviews (1 hour), and usability testing (1 hour) - will be enrolled for 3 hours.
- Year 2: 110 subjects who will participate in training (30 min), quantitative baseline assessment (45 min), brief follow-up assessments (11 times X 10 min), retrospective use assessment (30 min) and post-trial qualitative interviews (60 min) will be enrolled for 3-5 hours.

The duration anticipated to enroll all study subjects:
The anticipated duration for the enrollment of all study subjects constitutes 20 months. This includes 1) 6 months for stakeholder focus group, qualitative interviews, and usability testing, and 2) 14 months involving recruitment, training, pilot field testing of ERC-Nax system, post-intervention qualitative interviews, and post-trial qualitative user interviews.

The estimated date for the investigators to complete primary analyses for this study is July, 2019.

7) Study Endpoints

The primary endpoints of this study include the following:

1) Identifying barriers and facilitators of acceptance and use of a smartphone-based ERC naloxone intervention program;

2) Developing and testing the ERC-NAX, a smartphone app-based naxolone intervention;

3) Preparing groundwork for conducting a large-scale, multi-site implementation trial to measure the impacts of the intervention, including the potential positive effect on adherence levels (naloxone carrying); and provision of naloxone in overdose emergencies.

8) Procedures or Methods Involved

Screening

All participants will be screened at Prevention Point Philadelphia and meetings held by Angels in Motion. Interested individuals will be screened for study eligibility by an interviewer using a

scripted screening form. Individuals who meet the enrollment criteria and are interested in participating will be consented. baseline, study applicants will be asked a series of screening questions to determine their eligibility and safety of their participation in this study. While half of the sample will be active drug users, applicants who are clearly intoxicated will not be enrolled in the study.

At this stage, no identifying information will be collected and the answers to the questions will not be recorded. If the subject is deemed eligible, he or she will be asked if they are interested in participating in a longitudinal study that will involve one baseline assessment, 11 follow ups, and periodic retrospective follow ups.

If the person is interested in participating, he or she will be consented with an IRB-approved informed consent form. Upon enrollment, the interviewer will create a coded identifier for the participant. No personally identifying information will be collected from subjects to create this identifier.

Screener data will be collected to compare persons who qualify and enroll compared to those who qualify and refuse. Additionally, data on reasons for refusal will be collected.

Aim 1

Qualitative Interviews. We will conduct qualitative interviews with 10 stakeholders - 5 non-medical opioid users (NMOU) and 5 community members (CM) – to determine features that users want built into the app. Qualitative interviews will include questions focusing on the use of smartphones and smartphone applications, concerns about being part of an Emergency Response Community, concerns about using the ERC-NAX app during an overdose event, expected behaviors in different OD/response scenarios, and ideas for developing an optimal app.

Focus Groups. Three small focus groups will be held with combinations of 3 NMOU and 3 CM from the original 10 stakeholders at various points in the app development process so that stakeholders can provide feedback prior to finalizing the app. During focus groups, participants will be presented with application screen mockups to elicit user-requirements specific to the target populations. Data collection will be done using tablet/laptop computers. In addition, stakeholders will also be presented with a series of storyboard scenarios depicting ERC-NAX use in order to gauge pre-pilot willingness to participate and other key factors. One example of an interface question to be tested during focus groups is willingness to respond if others are responding (diffusion of responsibility), and how this should be reflected in the design. Figure 4 shows an alternative alert screen in which subjects are presented a map showing other members responding, in contrast to limiting information to just the location of the victim (Figure 1 Panel C). Knowledge that more people will be there to help may encourage participation (based on

Figure 4: Alternative alert design

shared identity theory), create impetus to 'get there first', or suppress urgency. Other scenarios will be tested if users prefer that the Talk button communicates only with the signaling victim, or created an open channel across all responders to this event. Scenario-based questions will allows us to control and manipulate alternative app designs with key variable interfaces, e.g., show member profile photos to identify responder, provide sound-beacon functions to locate victim at close range. This is a relatively fast data collection method which requires fewer resources than a prototype and allows us to explore a wider range of design issues.[75] Storyboarding is widely used as a technique to demonstrate system interfaces and contexts of use in a design process.[76,77] Similar approaches have been taken in the design of emergency medical information systems.[78,79] Additional features, such as a screen view through which NMOU can view the potential naloxone-carrying responders in their proximity (similar to Figure 2) will be presented to determine interest in possible modification of pre-use behavior, which answers the inherent question 'If I enter a state of OD and require help, is there anyone close by?'.

Usability testing. Heuristic evaluation will be performed with expert evaluators to identify and resolve potential usability issues before pilot testing begins. In addition, user testing will be performed with at least five NMOU and/or CM end users, who will be asked to perform a series of easy, medium, and difficult tasks while thinking aloud. One evaluator will facilitate the user tests while a second evaluator observes and takes notes. User tests will conclude with open-ended questions to gauge satisfaction with the application and willingness to use it in a real-world scenario. Data from user tests will be analyzed by both evaluators and solutions will be proposed and prioritized together with all investigators, based on how critical and how difficult each identified usability or technical issue will be to fix.

The primary goal of this phase is increased pilot suitability to both task and user population by improving usability and design of interface. Data will be put to immediate use to modify ERC-NAX design prior to pilot development. At the end of this stage, we will have a validated app design in support of expected behavior.

Aim 2

Following development of the ERC-NAX app we will initiate a structured and monitored launch of the system.

911 Alerts and ethical considerations. For the current study we propose to test an interface that automatically alerts 911 concurrent with the community alert. It is important to note that in no case does the pilot study bypass or eliminate response by EMS/First Responders. The guiding principles of the app design include automatic EMS alert by the app irrespective of expected ERC response. This functionality helps responders meet the apparent legal obligation to inform 911 upon providing naloxone. According to the current Standing Order for Pennsylvania,[86] a person administering naloxone is *"...immune from liability for giving naloxone if you believed the person was suffering from an opioid overdose (heroin or prescription pain medication) and you called for medical help/911 after giving the medication."*[86] Through the 'Good Samaritan' provision of PA State Act 139, bystanders are "*encouraged to call 911 for emergency medical services in the event an overdose is witnessed and to stay with the individual until help arrives. The provision offers certain criminal and civil protections to the caller so that they cannot get in trouble for being present, witnessing and reporting an overdose.*"[86]

App Diffusion and ERC-NAX Membership Requests. Active participation in the pilot will be limited to the 110 subject directly recruited and trained. However, it is important to understand effective ways to grow membership and app usage, determine how the app might diffuse from an initially seeded group of users, and collect location data from potentially active members. For that reason, the app will support open downloads and registrations but registrants outside the subject pool will be informed that their app is pending activation. Registrant data will be collected for potential full participation in follow-on studies.

App/Opioid Overdose Prevention Training. Following study enrollment and informed consenting process, overdose prevention training for all participants will occur at Prevention Point Philadelphia. Trainings, which will last approximately 30 minutes, will be delivered by PPP staff and consist of: overdose risk factors, steps to take in a witnessed overdose, and use of naloxone (Table 3). Participants will receive a doctor's prescription for naloxone, an instruction card, and two doses of NARCAN nasal spray (naloxone HCI, 4mg). During the same session, ERC-NAX app training sessions, which will last approximately 30 minutes, will be held for all study participants. In these sessions we will: validate proper installation of the app on each participant's smartphone; explain the alert mode operation of the app; explain the responder mode operation of the app; explain the EMS/911 functionality; have each participant initiate and alert and a response using the app's test mode.

Table 3: OD Prevention Training
1. Risk factors for overdose
2. Reducing risk for overdose
3. Recognizing an overdose
4. Steps to take if witnessing an overdose: sternum rub, call 911, provide rescue breathing, administer naloxone
5. Use of naloxone

Quantitative Baseline Assessment (QBA). The QBA, which take approximately 45 minutes to administer, will consist of 6 modules that capture key elements to be tracked over the course of the study (Table 4). Main predictors and outcomes will be assessed with validated standardized measures: psychological health [Brief Symptoms Inventory (BSI)];[91] physical health [12 Item Short Form Health Survey (SF-12)];[92] and Overdose Risk Behavior Scale.[93] Opioid and other drug misuse will be assessed with self-report questions that have been effective in prior studies.[89,94] Community members with limited drug use histories will skip sections of modules 3, 4, and 5. The QBA will be scripted using REDCap software, pre-tested, and administered during face-to-face interviews on a laptop computer.

Table 4: Quantitative Baseline Assessment (QBA) Modules & Select Key Measures (not exhaustive list of measures)
1. **Demographics** – age, gender, race/ethnicity, SES, educational, employment history, criminal justice history,
2. **Psychological/Physical Health History** – Chronic Pain Scale, BSI
3. **Opioid Use History/Practices** – Age of initiation, 30/90 day use, forms/doses, modes of administration
4. **Other Drug Use History/Practices** – Age of initiation of illegal/prescription drugs, tobacco and alcohol, 30/90 day use, modes of administration, polydrug use, drug treatment history
5. **Overdose History/Overdose Risk** – Personal overdose, lifetime witnessed overdose, Overdose Risk Behavior Scale
6. **Intentions to Use App** – Intentions to use app as caller, responder, or both

Brief Follow-Up Assessment (BFA). Following the QBA, BFA will be administered once per month for 11 months. The BFA will consist of a brief set of questions from modules 3 through 6 of the QBA covering recent opioid use, other drug use, experiencing/witnessing/responding to overdose, current possession of naloxone, and overdose risk behaviors. In addition, questions will focus on use of the app, such as rationale for use/nonuse during witnessed or experienced overdose events. Responders will receive vignettes that assess their ability to respond to a simulated overdose event. They will receive information such as: time of day, weather

conditions, location, distance, estimated walking time, gender, availability of other responders. Closed-ended items will assess ability to respond and barriers to respond if they are unavailable/unwilling. For example, we will explore geographic barriers (e.g. distance to user), characteristics of user (e.g. gender, age, race/ethnicity), time of event (i.e. unwilling to respond in the evening when it's dark or unwilling to go to a private residence), etc. The BFA will be launched via the ERC-NAX app and will offer participants a user friendly and intuitive interface for completing the brief via a secure project website. The BFA will take approximately 10 minutes to complete.

Retrospective Use of App Assessment (RUA). During the live pilot activity, the system will maintain a complete log of all user activity. We briefly describe the operation of the live system (complete details appear in the report by Schwartz and Khalemsky[63]). With the app installed and activated, the location of study participants is monitored at all times and securely stored in cloud servers. At any point in time, a participant can press the app's alert button initiating an intervention/urgent request for naloxone. Due to the nature of opioid overdose, we expect that often this alert will be initiated by a 'buddy' NMOU rather than by the overdosing individual. The app will acknowledge receipt of the alert and will instantly determine potential ERC members (both NMOU and CM) in the vicinity of relevant response. The alert will be sent to all available members with a request to respond. Members agreeing to respond will be guided to the member who initiated the alert. All alert and response activity (Table 5) will be logged automatically by the system for later analysis. Following each alert event, the participating members will be contacted for a Retrospective Use Assessment regarding their participation in the event and outcomes, including reactions to receiving alerts, such as response barriers and motivators for responders (Table 6) and event-precipitating factors for persons who overdose, such as quantity of drugs consumed, location of use, syringe sharing. Retrospective use assessments will be administered 4-48 hours after the event. Participants will receive a text message prompting them to initiate data entry beginning 4 hours after the event. An alert will cue them to respond every 4 hours until the assessment is completed or 48 hours have passed and the data entry window has close. Additionally, this data will enable us to identify users with different participation profiles to be further explored in end-of-trial qualitative interviews.

Table 5: Select Key Data Items collected per alert event from app (not exhaustive list of data items)

1. alert-time: date, time
2. alert-location: (x,y); street address
3. alerting-member ID
4. viable-members: set of IDs; set of locations
5. agreeing-members: set of IDs; set of locations
6. responding-members: set of IDs; set of locations
7. completing-members: set of IDs; set of locations
8. event-resolution-time: date/time

Table 6: Retrospective Use Assessment

RESPONDER	PERSONS-OVERDOSE
1. Caller or responder	1. Drugs consumed
2. Naloxone delivered	2. Route of administration
3. CBR delivered	3. Location of use
4. EMS arrival	4. Syringe/paraphernalia sharing
5. Motivators to respond	5. Motivators to use app
6. Barriers to respond	6. Barriers to use app

Qualitative Interviews. Over the course of the 12-month pilot of the app, we anticipate that participants will fall into four groups based upon their use of the app: caller; responder; both caller and responder; and neither caller or responder. We will conduct 20 qualitative interviews to understand and describe use (or lack of use) of the app: callers (n=5); responders (n=5); caller/responders (n=5); neither callers/responders (n=5). These 20 individuals will be selected from the larger sample of 110 participants. Depending upon the numbers in each group, efforts

will be made to select participants for qualitative interviews to obtain diversity across gender, race/ethnicity, and age. Interview topics will focus on experiences using the app, motivators/barriers to using the app, and impact of using the app on drug use (see Table 7). Qualitative interviews will be conducted face-to-face in a private or semi-private location, e.g., Prevention Point, that is convenient for the participant. Interviewees will receive a $50 incentive for participation.

Table 7: Qualitative Interview Modules
1. Experiences using the app
2. Motivators to using the app
3. Barriers to using the app
4. Impact of using app on patterns of drug use
5. Suggestions for app improvement

9) Data Banking

Following the completion of the study, data will be stored for three years on password-protected and digitally encrypted computers. Data analysis will also be performed on the same computers. Only PIs and IRB-approved research staff will have access to research datasets. After three years from the completion of the study, digitally-recorded screening survey forms and interview transcripts will be destroyed. Data will be stored for this amount of time to allow for the generation of publishable works from this research.

10) Data Management

Aim 1

Qualitative Interviews and Focus Groups. Individual and group interviews will be digitally recorded and transcribed. Qualitative data from interview transcripts will be entered into Atlas.ti (a qualitative software) and analyzed using inductive thematic analysis to identify themes that represent the most common opportunities and needs to be addressed during app development.

Usability testing

Descriptive quantitative data from user tests - five NMOU and/or CM – will be generated and analyzed. Solutions for app development will be proposed and prioritized together with all investigators, based on how critical and how difficult each identified usability or technical issue will be to fix.

Aim 2

Quantitative Baseline Assessment (QBA). SPSS and SAS will be used for data management and analysis. Procedures to clean quantitative data will include univariate analyses (e.g., mean, standard deviation) and patterns of correlation and covariance. Univariate statistics will be used to broadly examine the characteristics of the sample population and bivariate analyses (e.g., correlation analyses) will examine relationships among variables of interest. The quantitative baseline assessment data will be used in multiple ways to gain a descriptive understanding of the sample. For instance, a key goal is to describe different types of app users. By the end of the 12-month pilot, data will allow the sample to be divided into four groups: callers – persons who used the app to call for help; responders – persons who responded to a call; caller/responders – persons who both called and responded; and non-responders – persons who neither called nor responded. Participants will be sorted into these four groups and analyses will be conducted to characterize each group demographically and based on drug use history. The baseline

assessment, along with brief follow-up assessments, will be used to determine changes in app-related behavior of users over time.

Brief Follow-Up Assessment (BFA). Analyses will focus on understanding the extent to which the app was used when naloxone was needed and facilitators/barriers to its use. We will also examine participant engagement across key endpoints in overdose prevention including: (1) overdose risk (2) overdose experiences in which the app was not employed (3) witnessing overdose (4) administering naloxone, (5) app use while responding to an overdose; and (6) naloxone possession/refill. These endpoints represent critical moments when the app could be deployed to prevent overdose. A separate analysis will be conducted for each endpoint using summary statistics (frequency and percent with associated error terms). For each outcome, we will assess facilitators/barriers to identify factors that could be targeted with behavioral/educational interventions to increase app use at each stage. Combining quantitative baseline and follow-up assessments will provide a self-reported, longitudinal dataset. The data contains repeating observation on users, and enables a complete (all-users) study of behavior and expectation changes over time (compared to the baseline). Given the structure and completeness of the data, we can assess learning curves, engagement patterns, and perspectives (enthusiasm or exhaustion over time) while controlling for type of users (responders/ callers/ both), demographics, and drug use history. These data will enable us to establish patterns of drug use and associations with overdose as well as facilitators/barriers to using the app in situations when naloxone is needed.

Qualitative Interviews. All qualitative interviews will be transcribed by project staff and converted to Word documents. The analysis will involve: 1) the development of a descriptive coding frame; 2) memoing (writing down ideas as data are collected and analyzed); 3) comparison of memos with data collected from qualitative interviews; and 4) theory building. The coding frame will be developed through a series of a priori codes linked to interview questions, e.g., barriers to using the app, and open codes based upon probing questions linked emergent responses, e.g., stigma within user groups. Transcribed interviews (n=20) will be analyzed using ATLAS.ti software. The coding framework will be applied to developing broader themes connected to use of the app during the 12-month period. For instance, since sampling will divide respondents into four groups – callers, responders, caller/responders, and non-responders – qualitative analysis will be directed towards characterizing each group and determining differences between groups. The theme of "fear" or "trust" may be articulated by each group but in different ways – fear that police disrupt the scene among callers or fear that strangers may enter the scene among non-responders - that will impact use or non-use of the app.

Retrospective analysis of app registration and usage data. Event data, combined with the member location log, will allow behavioral and geospatial analysis of ERC-NAX usage providing insights into efficacy, ease of use, member availability, willingness to respond and other items important in advance of an R01. With ERC-NAX registration and usage data we will construct a comprehensive picture of participant alert and response behaviors, app diffusion, support network growth, and intervention potential. This includes a complete geo-location log of all participants over the full trial period, and details of each ERC alert event (sample of data items in Table 5).

The log data contains information of the actual use of the application by users, including (1) participation events: call open, call response, (2) geo-location upon use, and (3) demographic location of users. The combination of these data allow the analysis of *actual* use pattern, such as what type of users choose to open calls, at what time and condition, who responds to that call and when. Moreover, this data can be used to analyze nonusers, or users that respond to certain type of calls only, based on geographic proximity, temporality, or demographic match between the caller and responder. Relevant statistical analysis on log data includes survival analysis (unstructured repeating behavior): probability of call/response of users at a certain time point, given their type, and demographics.

Aim 3

In advance of a R01 multi-site randomized trial we will synthesize the results of the initial design, implementation, and pilot test. For each type of user (NMOU/CM), we will delineate the barriers and facilitators impacting adoption and use. Using system log usage data, we will group users into high/mid/low-usage cohorts (where low-usage includes users identified as having uninstalled or never activated the app) and analyze the interview data based on the cohort groupings. The efficacy of data collection through the app and EMI assessments will also be examined for lessons-learned leading to R01 modifications. Analysis of the pilot data will guide and inform modifications to the intervention design. A detailed study implementation manual will be drafted to support future multi-site studies. This will include sections on: participant recruitment; suggested retention strategies; app implementation and registration management; EMI methodology; survey methodology; log data collection procedures; and analytical models to be applied to data collected. Specific attention will be paid to:

Recruitment. A fundamental aspect of Aim 2 is the recruitment of 110 individuals into the study to pilot test the ERC-NAX app. As indicated, we will recruit 55 non-medical opioid users (who we anticipate will be the primary callers) and 55 community members (who we expect will be the primary responders). In both cases, individuals will need to: be trained in administering naloxone; carry naloxone; and own/carry smartphones. Assessing the ease of recruiting individuals in both groups in the targeted neighborhoods will be an indicator of broader interest and uptake of the app for the R01 study. Ultimately, the success of the app is contingent upon recruitment of both groups – persons witnessing an overdose who are willing to signal, and persons carrying naloxone who are willing to respond. Screener data will be used to determine characteristics of study participants vs. non-participants, and reasons for refusing participation will be analyzed. This quantitative data will be used to understand challenges towards recruiting a larger sample for a R01 study. We will also develop insights regarding app diffusion based on download and registration patterns beyond the initial 110 subjects which will be useful in designing the diffusion strategy for the R01 study.

Intervention Implementation. A critical success factor for the piloted intervention is the extent to which the subjects actually use the app, which generally depends on their perceptions of usefulness and ease of use. A fundamental goal of Aim 1 was to adapt the initial app design based on subject inputs to meet these goals. The activities of Aim 2 focused on assessing effectiveness of the app as reported by members in BFA and qualitative interviews. In Aim 3, we

revisit the design decisions made during the stages of Aim 1 in light of the results from Aim 2. This will enable modification of the app features and functions to hone suitability during emergency events, increase ease of use and perceived usefulness, and improve intervention implementation for the R01 study.

Retention/Adherence. Retaining both NMOU and CM in the study will be a key study outcome since the success of the app is contingent upon an ongoing critical mass of persons being able and willing to respond to an overdose when alerted. We anticipate a 10% attrition rate. Several necessary preconditions for responding to an overdose alert include: carrying naloxone; having a cellphone turned on; being located close enough to the event to respond in a timely manner; and being willing to respond to a stranger and/or unknown location. Qualitative interview data focusing on participants' experiences using the app, motivations to use the app, and barriers to using the app will illuminate factors pertaining to retention in study and ongoing use of the app. This qualitative data will be used to understand factors pertaining to study retention and adherence in using the app for the R01 study.

Assessment Processes

Interviews. Completion of the Brief Follow-Up interviews will be important to determine outcomes relating to drug use and overdose risk, possession of naloxone, and use of the app. Similarly, use of follow-up interviews would be a crucial part of a larger R01 study. Follow-up interview completion rates will be examined for each of the 110 participants. Statistical analysis will be used to determine characteristics of participants who complete follow-ups compared to those who do not. This quantitative data will be used to improve completion rates in the R01 study.

App usage. Analysis of the usage log data will be important to determine community behavior, response times and distances for responders, and potential for intervention based on member location for non-responders. This data will be used to study physical geographic distribution of members (both responders and non-responders) under the different conditions logged for each event. This quantitative data will be used to set baseline expectations for response behavior in the R01 study and inform the inclusion of new motivators in the R01 to extend the limits of response behavior.

Data Collection Efficacy. Quantitative data collected from study instruments, such as the Baseline Assessment, Brief Follow-Up, Retrospective Use of App, as well as logged alert and response activity, will be examined to determine the feasibility of collecting these data on larger scale for the R01. For instance, data from the Retrospective Use of App, which will be administered following use of the app, will be examined for missing data and data quality to determine the ideal period to administer the survey following an event.

Table 9: Working hypotheses for R01
H1 Intervention. Adoption of the ERC-NAX app by an OPP (trial) group will result in higher rates of naloxone use than in an OPP (control) group with an information-only app.
H2 Acceptance. Willingness to summon ERC member help in an overdose situation will result in increased emergency use of naloxone.
H3 Participation. Availability of the ERC-NAX application in a specific community will result in higher levels of naloxone OPP program participation for that community.

This proposal does not examine specific hypotheses that will become the subject of the planned R01 study to follow. However, it does validate the research constructs and methods through which the R01 hypotheses will be tested. For that reason, we present a list of several working hypotheses in Table 9. Aim 3 will specifically address the ability of an R01 trial to study the working hypotheses given the results of the pilot study.

Security of data

The study design will yield four primary types of data: quantitative data from the Quantitative Baseline and Follow-Up Assessments; qualitative data from the Qualitative Interviews and Focus Groups; retrospective data; smartphone use/app data; and participant tracking information.

The Quantitative Baseline and Follow-Up Assessments will yield a data file in REDCap that will be converted into an SPSS or SAS file during data analysis. The data file will primarily consist of coded numerical response to questions from the interview. The follow-up assessment will be launched via the ERC-NAX app and will offer participants a user friendly and intuitive interface for completing the brief via a secure project website.

Retrospective data. No participant identifying information will be stored in the smartphone. Retrospective responses will be directly entered into a secure study server through a project website with a standard web browser via an encrypted connection and any information entered will not be retained on the smartphone.

Smartphone use/app data. All app usage data will be automatically collected through the app which is purpose-built to gather relevant indicators. HIPAA-compliant servers will log all activity and ensure security of Protected Health Information (PHI). Secure-server stored data includes geolocation and emergency alert/response information referenced only by unique subject identifiers and containing no identifiable private information (IPI). A single system table linking identifiers to IPI will be maintained and secured separately following the most stringent data security standards. No event history data will be stored on individual smartphones.

Qualitative data from qualitative interviews and focus groups. All the qualitative and focus groups interviews will be digitally recorded. Interviews will be transcribed by a New York-based company (Transcript Divas) within one month of the interview and converted into an electronic Word document. During the transcription process, all identifying information revealed by the subject – about his/herself or others - will be removed. The digital file will be destroyed after determining that an accurate transcript has been created from the digital recording (within one month of developing the transcript). The electronic transcript may also be printed as a hard copy or paper copy for analysis. Each paper copy will be labeled with the coded identifier assigned at the time of interview, stored in an individual folder, and locked in a file cabinet when not in use. Each interview note will be labeled with the coded identifier assigned at the time of interview, stored in an individual folder, and locked in a file cabinet when not in use. The digital file will be destroyed after determining that accurate notes have been created from the digital recording (within one month of developing the transcript).

Participants will be asked to provide contact information including: current residence; home, office, and cellular phone numbers; pager number; email/Facebook addresses; and the names, addresses, and phone number of immediate relatives and of an unrelated friend. This contact and

locating information will be entered and stored in a password-protected Access database and updated throughout the project period. Tracking information will be collected at baseline onto a paper tracking form. The paper copy will be destroyed after the information has been stored electronically.

Access to Individually Identifiable Private Information. Only individuals at Drexel will have access to individual identifiable private information. At Drexel, the following individuals will have access: Lankenau (Principal Investigator); Roth (Co-Investigator); Marcu (Co-Investigator) and TBN (Data Manager). All research staff will be trained on the proper procedures for handling confidential data.

11) Provisions to Monitor the Data to Ensure the Safety of Subjects

An external Data and Safety Monitoring Board (DSMB) will be established to oversee the safety of participants as part of the overall Data and Safety Monitoring Plan. The DSMB will be established within the first two months of the study start date and will consist of three members with the following expertise: a clinician (MD) with experience running clinical trials; a bioethicist; and a community member with direct experience with the problem of opioid misuse and/or overdose. Any potential adverse events (AE) relating to use of the ERC-NAX app will be documented and reported to the Principal Investigators and DSMB. The DSMB will review any potential AE to determine if they meet criteria for serious adverse events (SAE). Any SAE, whether or not related to ERC-NAX app, will be reported to the Principal Investigators, the IRB, and NIDA. The DSMB will convene at least twice during the 12-month data collection period to query the Principal Investigators about participant safety if no AE are reported.

12) Withdrawal of Subjects

A study participant may be asked to withdraw from the study due to a serious adverse event (SAE) if the Principal Investigator determines it is the best interest of the participant's safety. In case a participant either withdraws from the study or PI decides to discontinue a participant, the participant will have appropriate follow-up. Monitoring will continue until the problem has been resolved or stabilized with no further change expected, or is clearly unrelated to study intervention.

In the event of participant withdrawal, at any point during survey or interview process, data will be immediately destroyed. If the participant wishes to stop survey or interview, but does not want data from survey or interview destroyed, collected data will used, but a survey or interview will be considered incomplete.

If a participant takes part in an interview, but later decides to withdraw her data, the interview will be destroyed.

13) Risks to Subjects

The possible risks to subjects involved in this research include the potential loss of confidentiality, potential distress caused by interview questions, and potential distress caused by responding to a drug overdose.

Drug users engage in a variety of illegal activities apart from use of illicit substances, such as drug selling, violent behaviors, and other crimes, which could be recorded during interviews. These individuals could be at risk for arrest from police or retribution from others if the confidentiality of the data were to be compromised. Subjects will also provide self-reported information about their HIV status and HIV-related risk behavior. There is a risk that others not involved in the study could learn this sensitive information if the confidentiality of the interviews is compromised. However, no data will be stored on participant's smartphones or through EMA data collection methods. Our research shows that active drug users perceive few potentials harms and many benefits associated with participation in a longitudinal EMA study of drug use.[69]

To protect against a loss of confidentiality, all interview data, and tracking data will be identified by the coded identifiers, password-protected, and/or stored in locked filing cabinets. Identifying information will be removed from qualitative interviews. All staff will be trained in confidentiality procedures. The project will obtain a Federal Certificate of Confidentiality, and interviewers will carry it at all times when conducting research. In our past NIH studies involving similar high-risk populations, these procedures have proven effective, and we have not had any adverse events to report to the IRB.

Another potential risk to subjects is the experience of emotional distress that may result from responding to a drug overdose. However, our prior research on bystanders responding to overdose events with naloxone did not indicate any adverse events.[9,60] The study staff who conduct interviews will refer emotionally distressed study participants to a qualified case manager or mental health worker for assessment and care. A similar protocol is currently in place for a current R01 study of young drug users.

For the current study we propose to test an interface that automatically alerts 911 concurrent with the community alert. It is important to note that in no case does the pilot study bypass or eliminate response by EMS/First Responders. The guiding principles of the app design include automatic EMS alert by the app irrespective of expected ERC response. This functionality helps responders meet the apparent legal obligation to inform 911 upon providing naloxone.

During the course of retrospective qualitative interviews, follow-up interviews, or assessments, interviewers and/or data analyst will check for events relating to use of the ERC-NAX that had any adverse consequence for the study participant or others using the app. All adverse events (AE) occurring during the course of the study will be collected, documented, and reported to the Principal Investigator within 24 hours of discovering the event. Each week the Principal Investigator will review AE from the prior week for events that were reported as new or continuing. The study investigators will follow all AE to the point of a satisfactory resolution. In any addition, quantitative and qualitative data will be monitored by random inspection monthly to ascertain any possible AE that went unreported to the PI.

All AE will be assessed to determine if they meet criteria for serious adverse events (SAE). SAE will be systematically evaluated. Any SAE, whether or not related to ERC-NAX app, will be reported to the Drexel IRB and NIDA. The initial SAE report will be followed by submission of

a completed SAE report to both institutions. Outcome of SAE will be periodically reported to NIDA. A summary of the SAE that occurred during the previous year will be included in the annual progress report to the Drexel IRB and NIDA.

Dr. Lankenau will be responsible for reporting adverse events. Adverse events deemed to be serious and unexpected and possibly related to participation in the study will be reported promptly to the IRB. If it is believed that the reported events merit change to the consent form, then the Dr. Lankenau will submit a revised consent form to the IRB for review and approval.

Dr. Lankenau and co-investigators are experienced researchers who are accustomed to working with high-risk populations, including persons at risk for overdose. All interviewers will be trained by Dr. Lankenau to screen for intoxicated individuals and how to identify emotional distress. This information will be discussed during staff meetings, and staff training will be ongoing. In the event that a research subject becomes emotionally distressed during an interview, interviewers will stop the interview immediately and the interviewer will provide an escort to whatever emergency services are necessary. Whenever specifically requested by the subject, interviewers will provide a direct telephone referral and escort the subject to appropriate services in the community.

Overall, the risks are similar to anyone who volunteers to be trained in overdose prevention, carries naloxone, and responds to an overdose. We believe that these planned procedures in conjunction with the potential benefits of this study outweigh the potential risks.

14) Potential Benefits to Subjects

There is no direct benefit to subjects; however we anticipate that this research will be beneficial for those enrolled in the study in several indirect ways. The ERC-Nax and related overdose prevention training has the potential to save lives of enrolled participants, persons in their social network, or strangers. During the interview process it is possible that participants will identify behaviors or circumstances that increase their risk for negative health outcomes, which can lead to behavior change. Interviewers will provide a direct referral and/or escort to appropriate mental health and social services if requested.

15) Vulnerable Populations

Does not apply

16) Multi-Site Research

Does not apply

17) Community-Based Participatory Research

Our approach will involve user-centered design,[72] participatory design,[73] and community-based participatory research[74] to engage end users and stakeholders in the design of the ERC-NAX app. Guided by emergent themes from qualitative data collection and analysis, ERX-NAX mockups and prototypes will be generated using a rapid iteration process. Two community-based organizations, Angels in Motion and Prevention Point Philadelphia, will assist with the recruitment of community members (CM) and non-medical opioid users (NMOU) in both the development of the ERC-NAX app, e.g., stakeholders, as well as during recruitment of study

participants to test the app. Starting with low-fidelity prototypes, feedback will be solicited from stakeholders on an ongoing basis and iteration will continue until a high-fidelity prototype has been generated that stakeholders do not identify issues with, and that provides enough specification to guide software development. These approaches ensure that the resulting solution and interface will be usable, feasible, and adoptable. End users and stakeholders will co-create an app that meets their needs relating to overdose response and realistically fits into their everyday lives. Using an iterative process, data collection and analysis will occur concurrently during Year 1 to support the development of the app and will involve several components, including qualitative interviews, focus groups, and usability testing.

18) Sharing of Results with Subjects

Presentations on study results will be conducted at both Prevention Point Philadelphia and Angels in Motion. Study participants will be contacted and encouraged to attend these presentations for their insight and feedback on study results.

19) Setting

Recruitment of NMOU will be facilitated by Prevention Point Philadelphia (PPP) and conducted at their Kensington facility. PPP serves the most vulnerable and hard-to-reach populations of Philadelphia, including people who use drugs and sex workers. The agency takes a harm reduction approach to high risk behavior by providing safety measures for people who are at high risk for contracting HIV/AIDS, hepatitis C, and other blood-borne diseases, including overdose prevention trainings. CM will be recruited through Angels in Motion, a community-based group located in Kensington that is comprised of individual community members and hold bimonthly meetings.

20) Resources Available

Two community-based organizations, Angels in Motion and Prevention Point Philadelphia, will assist with the recruitment of 55 community members (CM) and 55 non-medical opioid users (NMOU). Feasibility of recruitment is assured by the fact that both Angels in Motion and Prevention Point Philadelphia have members or clients that greatly exceed the number of subjects enrolled to be enrolled in the study. The Executive Director of Prevention Point Philadelphia (Jose Benitez) and the President of Angels in Motion (Carol Rostucher) have reviewed the study aims and support for this research (see Appendix - Letters of Support).

Staff

Research Team: An experienced interdisciplinary team brings together the diverse knowledge and skills required for this proposal. Addiction sociology and public health (Prof. Lankenau and Dr. Roth), information systems, mHealth systems, and online social networks (Prof. Schwartz and Dr. Yahav), mobile app design and human-computer interaction (Prof. Marcu), each play a fundamental part of this effort. Qualitative and quantitative data collected and analyzed in this project require techniques involving EMA/EMI, social network analysis, data clustering and geo-spatial analysis. The team will conduct weekly skype meetings, semi-annual face-to-face sessions, and utilize a secure document/data-sharing and collaboration platform.

Dr. Stephen Lankenau is a Professor in the Department of Community Health and Prevention at Drexel University's Dornsife School of Public Health. A sociologist by training, his research focuses on the use and misuse of substances at the forefront of current public health concerns, including marijuana and opioids, and associated morbidities, such as overdose, HIV, HCV, and drug dependence. The problem of opioid overdose and prevention has been a focal point of his studies conducted in Philadelphia and Los Angeles since 2009. Dr. Lankenau's methodological approach to public health research combines qualitative and quantitative techniques into integrated mixed method designs. Dr. Lankenau will lead the data collection of study participants in Philadelphia, lead the qualitative analysis, and be responsible for human subjects protection. Dr. Lankenau will be supported 15% time in Years 1-3.

Dr. David Schwartz is director of the Social Intelligence Lab and Professor of Information Systems at Bar-Ilan University, Israel, where he leads the Emergency Response Community (ERC) initiative. The ERC program, initiated in 2013, leverages the convergence of mobile smartphone technologies and social networks to build and study location-aware emergency response platforms – a novel form of ecological momentary intervention. A number of leading medical experts have joined the initiative, providing medical guidance, including Prof. Dr. Abdel Bellou (former president of the European Society for Emergency Medicine and currently Disaster Medicine Fellow at BIDMC/Harvard), and Prof. Dr. Nikos Papadopoulos (president of the European Association for Allergy and Clinical Immunology). The supply of adrenaline auto-injectors in incidents of anaphylaxis became the first targeted application of ERC, which Dr. Schwartz will continue to study and develop alongside this new overdose-reversal study. Dr. Schwartz will lead the design efforts to adapt the app specification and system architecture, ensure that the pilot follows the principles established for ERCs, contribute to the study of app usage barriers/motivators, and lead quantitative geo-spatial analysis of data logs. Dr. Schwartz will be supported at 15% in Years 1-3.

Dr. Alexis Roth is an Assistant Professor in the Department of Community Health & Prevention at Drexel University's Dornsife School of Public Health. Her research is focused on individual, social and environmental factors that influence health disparities among vulnerable populations living in urban settings. She has extensive experience in the use of mobile phone technology to monitor event-level HIV risk and drug use, mixed methods research, and the development and evaluation of structural interventions to improve healthcare utilization among populations unlikely to seek clinical care. Additionally, she has expertise in the ethical considerations for using ecological momentary assessment with vulnerable populations, including opioid users. Dr. Roth will be supported at 10% in Years 2-3.

Dr. Inbal Yahav is an Assistant Professor at the Graduate School of Business Administration, Bar-Ilan University, Israel. Her research interests lie in the areas of statistical modeling and social media, with a focus on users' behavior in social networks, interactions and dynamics between users, and statistical modeling of heterogeneous behaviors. Her research to-date focuses on two domains. The first is cyber security and privacy, and in specific privacy unawareness and unintentional information leakage in social networks. The second is statistical modeling of sub-populations in Big Data. She has presented her work at multiple Information Systems conferences and published papers in books and journals. She is currently serving as an Associate Editor of the Decision Sciences Journal and the Big Data Journal. Dr. Yahav will be supported at 10% in Years 1-3.

Dr. Gabriela Marcu is an Assistant Professor in the College of Computing and Informatics and Research Fellow with the A.J. Drexel Autism Institute. She has 8 years of experience with community-based participatory research for the development of novel behavioral interventions delivered via mobile devices. She is currently PI or Co-PI on three projects in which she is responsible for leading the design, development, and evaluation of mobile applications, including ecological momentary interventions. Additionally, she was principal designer of a smartphone intervention for the treatment of bipolar disorder, which was successfully used in a clinical trial. Dr. Marcu directs the Empathic Design and Technology Research Group, a multidisciplinary group of software developers, interface designers, and qualitative social scientists who work collaboratively on mHealth development projects from beginning to end of the software life cycle. Dr. Marcu will be supported at 20% during the summer months in Years 1-3.

Facilities

At Drexel University, the PI and Co-Investigator each have 300 sq. ft. office is located on the 4th floor of the Nesbitt Building, which is home to the School of Public Health's Department of Community Health and Prevention. It is equipped with chairs, desk, bookcases, two locking filing cabinets, and hardwired high-speed internet access. Each member of the research team each has a 60 sq. ft. cubicle equipped with chairs, desk, locking filing cabinets, and high-speed internet access. All computers are connected to laser printers. These facilities ensure that the PI and research team have the necessary space and equipment to store data, analyze results, and prepare manuscripts for publication.

At Bar-Ilan University, the PI and Co-investor each have 160 sq. ft. offices located on the 3rd floor of the Daniel S. Abraham Center of Economics and Business Building, which is home to the Graduate School of Business Administration's Information Systems Department. Each is equipped with chairs, desk, bookcases, two locking filing cabinets, and hardwired high-speed internet access. All computers are connected to laser printers. These facilities ensure that the has the necessary space and equipment to store data, analyze results, and prepare manuscripts for publication.

Prevention Point Philadelphia is an excellent setting for drug users' screening, surveying, and interviewing. The agency has 8 private rooms usually used for case-management sessions or medical services (for example, HIV or Hepatitis C testing); one of these rooms or another private space in the PPP office will be available for survey or interviewing. PPP is staffed with experienced case-managers who can assist study participants in case of emotional distress. PPP also houses a clinic with medical staff able to assist participants with acute health problems. Additionally, the agency's staff and the student researcher herself are trained to recognize overdose signs and administer naloxone (opioid antidote) in case there is overdose emergency during survey or interviewing. In case the interview will be scheduled outside of the PPP office, a mutually acceptable location (café or chain-restaurant) will be chosen within walking distance from the PPP office or mobile van, so that the student researcher is able to promptly reach PPP qualified staff in case of a medical emergency

Medical/Psychological Resources/Training

Dr. Lankenau and co-investigators are experienced researchers who are accustomed to working with high-risk populations, including persons at risk for overdose. All interviewers will be

trained by Dr. Lankenau to screen for intoxicated individuals and how to identify emotional distress. This information will be discussed during staff meetings, and staff training will be ongoing. In the event that a research subject becomes emotionally distressed during an interview, interviewers will stop the interview immediately and the interviewer will provide an escort to whatever emergency services are necessary. Whenever specifically requested by the subject, interviewers will provide a direct telephone referral and escort the subject to appropriate services in the community. All adverse events (AE) occurring during the course of the study will be collected, documented, and reported to the Principal Investigator within 24 hours of discovering the event.

21) Prior Approvals

Approvals from Drexel University's Institutional Review Board and a Federal Certificate of Confidentiality will be obtained prior to commencing recruitment and data collection for this research.

22) Recruitment Methods

Recruitment Plan. Participants (non-medical opioid users and community members) will be sampled using targeted and chain referral sampling,[87,88] which was deployed effectively in previous PI studies.[89,90] Targeted sampling focuses on particular locations containing the population of interest. In this case, Prevention Point Philadelphia and Angels in Motion will be targeted to enroll NMOU and CM, respectively. Community members may also be enrolled from PPP staff. Chain-referral sampling, which utilizes currently enrolled participants to refer others within their network, consciously attempts to sample from multiple networks to increases the diversity of the sample. A key strength of this sampling methodology is controlling screening and enrollment so that the sample is diverse in terms of gender, race, and age.[89]

Payments:

- Each individual screened will receive a $3 gift card.
- Enrolled participants will receive $25 for the baseline interview and participation in the OPP.
- Participants will receive $5 for each completed BFA
- Qualitative interviewees will receive a $50 incentive for participation.

23) Number of Subjects

10 stakeholders will take part in qualitative interviews, including 5 non-medical opioid users (NMOU) and 5 community members (CM). Of the 10 stakeholders, 6 people (3 NMOU and 3 CM) will participate in focus groups.

110 participants (55 NMOU and 55 CM) will take part in Quantitative Baseline Assessments (QBA), Brief Follow-Up Assessments (BFA), and Retrospective Use Assessment (RUA) following use of the app. A subset of the 110 participants, 20 people, will be recruited for a

Qualitative Interview based upon use of the app including 5 callers, 5 responders, 5 caller/responders, and 5 people who are neither callers/responders.

Retention Strategies for Follow-Up and Attrition. Study investigators fully appreciate the challenges associated with tracking and retaining participants in a longitudinal study, particularly drug users. We are practiced at successfully retaining participants for follow-up interviews based upon employing tracking protocols in previous studies,[90] in which many subjects were hard-to-reach due to substance use. Key retention strategies include: collecting extensive tracking information at baseline, including email and social media info; storing tracking information in retrievable Access database; conducting monthly follow-up interviews with incentives ($5); training staff on the importance of retention. Despite these tracking efforts, we are anticipating some participant attrition. Based upon our previous studies, we are predicting 10% attrition over the course of the year-long study resulting in a final sample of 100.

24) Confidentiality

Does not apply (not a multi-site study)

25) Provisions to Protect the Privacy Interests of Subjects

Subjects' privacy interests will be protected through the use of informed consent process, as well as by not collecting their identifying data. The interviewees will be assured that sensitive information about their drug use, overdose experiences, street-related activities, and violence in their lives is expected to be offered voluntarily and will be treated with strict confidentiality. The participants will be informed of their rights, including the right to withdraw from the study at any point and not answer questions the participant chooses not to.

Additionally, it is expected that the majority of qualitative interviews will be held at a private room at the PPP office that should also help participants feel at ease. In cases when participants are recruited at the PPP van and available for interview immediately after survey, a quiet semi-private location (café or chain restaurant) will be chosen for interview. If the participant does not feel comfortable at that place, she will be scheduled an interview at the PPP office or other mutually accepted location at another time/day.

The research team (PI and the student researcher) will not be permitted to access any sources of information about the subjects.

26) Compensation for Research-Related Injury

Does not apply (the research does not involve more than minimal risk).

27) Economic Burden to Subjects

The participation in the research does not involve any economic burden to participants. Interviews for eligible participants will be held at their convenience.

28) Consent Process

Participants will be consented with one of two consent forms. One consent form will be used to 10 consent participants for stakeholder interviews during Year 1. This form will consent participants to engage in the following research activities: focus groups, qualitative interviews, and usability testing. A second consent form will be used to consent 110 participants during Year 2 to engage in the following research activities: Quantitative Baseline Assessment (QBA); Brief Follow-Up Assessment (BFA); Retrospective Use Assessments; and Qualitative Interviews.

Prior to enrolling a subject in Year 1 or Year 2 activities, study interviewer will conduct the consent process using a Consent Form. The interviewer will read the Consent Form out loud and ask the participant to follow along. The interviewer will ask questions about the subject's comprehension during this process and will ensure that all the subject's questions have been answered before asking the subject one final time whether he/she wants to participate in the study. The consenting participant will sign the Consent Form as will the interviewer. Both participant and interviewer will keep a copy of the signed Consent Form. Following the interview, the interviewer will place the consent form in a locked filing cabinet at Drexel.

In all cases, the process of obtaining informed consent will only occur after the potential subject has been given a description of the project, has been screened for eligibility, and a semi-private interviewing location has been secured. Trained interviewers will obtain verbal consent from all subjects who participate in interviews. Consent forms will contain a discussion of the following: the study sponsor; the goals and objective of the study; responsibilities of participating in the study; the use and outcome of study data; the risks involved in participation; the benefits of participation; the compensation for participation; the content of information provided to others (confidentiality); the voluntary nature of participation; and the rights of study participants. Interviewers will provide each subject with a consent form and read through the entire document. After the subject indicates that he or she understands all sections of the consent form, he or she will indicate his/her verbal consent to participate, and the interviewer will document this verbal consent. The interviewer will offer a copy of the consent form to the enrolled subject. At that point, the subject will be formally enrolled in the study, and the interviewer will proceed with the interview. This consent form will provide consent for the baseline and subsequent follow-up interviews. Participants will be reminded of their rights as research participants during follow-up interviews in the scripted online interview or verbally during face-to-face interviews.

Non-English Speaking Subjects

Does not apply

Waiver or Alteration of the Consent and Authorization Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

Does not apply

Subjects who are not yet adults (infants, children, teenagers)

Does not apply

Cognitively Impaired Adults

Does not apply

Adults Unable to Consent

Does not apply

29) Process to Document Consent in Writing

The study will be following SOP: Written Documentation of Consent (HRP-091).

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Appendix – Letters of Support

1. Prevention Point Philadelphia
2. Angels in Motion

PREVENTION POINT
2913-15 Kensington Ave., Philadelphia, PA 19134
Phone: 215-634-5272; Fax: 215-634-5271

November 30, 2016

Stephen E Lankenau, PhD
Dornsife School of Public Health
Drexel University
3215 Market Street, Room 411
Philadelphia, PA 19104

Dear Steve,

I am writing this letter to express my support for your R34 application entitled "Piloting a naloxone intervention in an emergency response community to reduce opioid overdoses in Philadelphia." Prevention Point Philadelphia, a community-based harm reduction organization, has been providing overdose prevention training and distributing free naloxone to individuals at risk for overdose since 2006. I see this as an important proposal since opioid overdose is a significant health problem in Philadelphia, naloxone is increasingly available to reverse overdoses, and persons trained by Prevention Point are willing to respond to drug overdoses. The proposed mobile naloxone application that can assist bystanders in responding to drug overdoses is the next logical step in addressing this epidemic.

Prevention Point's storefront office is located in the Kensington neighborhood of Philadelphia, which has some of the highest rates of opioid overdose in the city. Our clients include active users of heroin and prescription opioids who are at high risk of overdose and have been trained in overdose prevention. Given that our office is located in the targeted area of your proposed study and we service active heroin/opioid users who have been equipped with naloxone, we can assist you and your team in recruiting non-medical opioid users (NMOU) for both the pilot and implementation phase of the naloxone application trial. Given our assistance, I am fully confident that your team will be able to recruit and interview the requisite number of opioid users into the study.

I have been discussing aspects of this study with both you and Dr. Schwartz over the past year and am encouraged about its potential towards saving lives. Once developed, the mobile naloxone application could offer rapid response to opioid overdose in our community as well as provide real-time information on overdose hotspots in Kensington and elsewhere in Philadelphia.

Lastly, Prevention Point has been partnering with you and your graduate students on the problem of opioid overdose in Philadelphia since 2010. We view this grant application as an extension of our ongoing collaborations with you and Drexel University and look forward to working together on this project.

Respectfully,

Jose A. Benitez MSW
Executive Director

Carol Rostucher
2024 Ripley Street • Philadelphia, PA 19152 • 215-501-3357

November 30, 2016

Stephen E Lankenau, PhD
Dornsife School of Public Health
Drexel University
3215 Market Street, Room 411
Philadelphia, PA 19104

Dear Steve,

This letter is in support of your R34 application entitled "Piloting a naloxone intervention in an emergency response community to reduce opioid overdoses in Philadelphia." Angels in Motion is a community-based organization located in Philadelphia that has been providing street outreach support to persons suffering from drug addiction since 2015. Angels in Motion holds twice-monthly community meetings to help spread awareness about drug addiction and offers support to families, friends, and loved ones that have been effected by this disease. The problem of drug overdose has been a particular focus of our outreach efforts.

Angels in Motion do a majority of their street outreach in the Kensington neighborhood of Philadelphia, which has a long-standing problem of heroin use and drug overdose. Angels in Motion volunteers are trained in overdose prevention, carry naloxone, and own smartphones. Since our volunteers service the targeted area of your proposed study and are trained in the use of naloxone, we can assist you and your team in recruiting community members (CM) for both the pilot and implementation phase of the naloxone application trial. Given our assistance, I am very confident that your team will be able to recruit and interview the requisite number of community members into the study.

Over the past year, I have been discussing aspects of this study with you and am optimistic about its potential towards saving lives. I am hopeful that proposed mobile naloxone application could increase the response time to drug overdoses in our community and encourage more community

members to receive overdose prevention training. I see this as an innovative proposal since it utilizes the concept of Emergency Response Community (ERC) and applies it to community members who are trained in overdose response and carry naloxone. The ERC approach is ideally suited to support, facilitate, and encourage naloxone use for overdose reversal. Helping community members respond to drug overdoses through the proposed mobile naloxone application is an important step in addressing the problem of overdose in Philadelphia.

I have enjoyed getting to know you over the past year through meetings at Prevention Point and while attending meetings for the recently created Overdose Prevention Task Force. I see this grant application as opportunity to develop a new collaboration with you and Drexel University and look forward to working together on this project.

Sincerely,

Carol Rostucher
President/ Founder