PROTOCOLS

kuali

UC San Diego
INSTITUTIONAL REVIEW BOARD ADMINISTRATION

Date: Friday, January 13th 2023

PI: STRATHDEE, STEFFANIE

IRB# 801950, Version 10 in KIRB

Title: LinkUP: COVID-19 Intervention for underserved populations participating in parent study Proyecto La Frontera

Type: Renewed

Review: Full Board by IRB A (IRB00000354)

Decision: Thursday, January 12th 2023, valid through 11:59 pm (Pacific) Monday, February 5th 2024

The above review is complete with the following outcomes:

The continuing review for the above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts.

The IRB determined that this project presents no more than minimal risk to human subjects in that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

It was determined that future renewal submissions for this study can be reviewed through the expedited review procedure as authorized by 45 CFR 46.110 and 21 CFR 56.110 and falls under the following research category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

ADMINISTRATIVE NOTE: Submit an amendment within the next 30 days regarding the following: The Research Plan states, "Although the LinkUP trial is not powered to assess efficacy, we will conduct an intent-to-treat analysis following CONSORT guidelines[24] and register it at clinicaltrials.gov before enrollment."
1. Please confirm this study is registered with clinical trials in the amendment description.
2. Update the Kuali Clinical Trial Section to select "yes" on the question about clinicaltrials.gov.
3. Update the consent forms to include UCSD's template language about clinical trials, which states," A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time."

NOTE: IRB approval does not constitute other institutional required approvals. In the conduct of this research, the PI and study team must abide by UC San Diego PPM 100-5 (Responsibilities Section, Item D) and obtain any other approvals or permissions required by applicable laws or university policies.

If your study is a clinical trial you are reminded that applicable clinical trials must be registered on ClinicalTrials.gov. For more information or assistance, visit https://blink.ucsd.edu/sponsor/rci/clinical-trials.html or email the Research Compliance and Integrity Office at ctgov@ucsd.edu.

The following attachments are approved or acknowledged as part of this review:

Attachments

LINKUPINTERVENTION_RESEARCH_PLAN_03.23.2022 clean.docx	Protocol	Revised Research Plan (Clean)
Revised_Radx-UP_Intervention_ ICF_English_03.23.2022 clean.pdf	Informed Consent/Parental Permission	Revised English ICF (Clean)
Revised Radx-UP_Intervention_ ICF_Spanish_02.04.2022_clean.pdf	Informed Consent/Parental Permission	Revised Spanish ICF (Translated by Alicia Harvey-Vera. PI attests to the accuracy of her translation skills) (Clean)
Data Safety and Monitoring Board-LinkUP final-05.14.docx	Other	DSMB Plan
LINKUPINTERVENTION_RESEARCH_PLAN_03.23.2022.docx	Protocol	Revised Research Plan (Tracked Changes)
Revised Radx-UP_Intervention_ ICF_Spanish_02.04.2022_tracked_changes.doc	Informed Consent/Parental Permission	Revised Spanish ICF (Tracked Changes)
Revised_Radx-UP_Intervention_ ICF_English_03.23.2022.doc	Informed Consent/Parental Permission	Revised English ICF (Tracked Changes)

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

LinkUP: COVID-19 Intervention for underserved populations participating in parent study Proyecto La Frontera (UCSD IRB #191390).

2. PRINCIPAL INVESTIGATOR

Steffanie Strathdee, Ph.D., Distinguished Professor and Harold Simon Chair, Associate Dean of Global Health Sciences, Division of Infectious Disease and Global Public Health, UCSD Department of Medicine

3. FACILITIES

The UCSD investigators and staff for this project have offices on the main UCSD campus (La Jolla and 3500 5th Avenue 'Webster Building').

The field operations for the evaluation component of this study will be carried out in part on the streets of San Diego County by UCSD's La Frontera staff. Operating on a mobile van, this component of the study will determine participant eligibility, obtain informed consent, refer consenting participants to our community partner (OnPoint), and conduct a prospective evaluation of the LinkUP intervention.

Sera are batched and delivered to Genalyte (San Diego, CA), a CLIA-certified lab that has obtained Emergency Use Authorization for their SARS-CoV-2 serology assay.

This project will be conducted in collaboration with a community partner, the Harm Reduction Coalition of San Diego (HRCSD) which operates a mobile Syringe Exchange Program (SSP) called OnPoint at 4 locations across San Diego. These 4 locations will be sites where participants will be offered rapid COVID19 antigen and/or SARS-CoV-2 PCR tests as part of their standard of care, and where participants will either receive the active version of the LinkUP intervention (education plus motivational interviewing) or the didactic version of the LinkUP intervention (control condition: education only). Both versions of the LinkUP intervention, as well as COVID testing, will be conducted by staff of OnPoint. Participants opting for SARS-CoV-2 PCR tests, or those testing positive on COVID rapid antigen tests will have their confirmatory PCR tests conducted by a certified lab of the California Department of Public Health (CDPH). Participants opting for vaccination will be referred participants for vaccine to nearby clinics. Because the HRCSD will be engaged in research activities such as administering the LinkUP intervention as part of this project, they will be reliant on UCSD which will serve as the IRB of record for this site, per NIH Single IRB mandate.

Data analysis for this study will be conducted by UCSD Staff at the Webster Building in Hillcrest. Analysis of de-identified data will also be conducted by the RADxUP Consortium Data Center at Duke University. LinkUP is a part of the RADxUP consortium, which is a network of U.S. research institutions supported by the US National Institutes of Health through the American Recovery Act. RADxUP aims to increase access to COVID19 testing and vaccination among marginalized communities across the US and is attempting to identify best practices based on information collected and shared across the consortium. The RADxUP Data Coordinating Center is based at Duke University in North Carolina

4. ESTIMATED DURATION OF THE STUDY

Two years: March 1 2021- August 30, 2023.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Preliminary data from the parent study, La Frontera, have shown that people who inject drugs (PWID) in San Diego county are at high risk of COVID-19, yet have very low levels of COVID testing and vaccination. The goal of the present study is to evaluate a pilot intervention (LinkUP) to improve the uptake of COVID-19 testing and vaccination among PWID in San Diego County. Results will be shared with RADxUP consortium members, policymakers and program planners in California and across the US and used to estimate effect sizes for a future efficacy trial. Our study will inform efforts to leverage any of the 185 SSPs around the US as 'touchpoints' to reach marginalized communities, strengthening the nation's pandemic preparedness infrastructure to reduce COVID-19 health disparities.

6. SPECIFIC AIMS

Together with our community partner, the HRCSD's OnPoint, a mobile SSP, we will evaluate develop and evaluate an intervention to improve uptake of COVID-19 testing and vaccination. Our Study Aims are :

1) To adapt an existing behavioral intervention incorporating motivational interviewing (MI) to improve uptake of HIV pre-exposure prophylaxis among people who inject drugs (PWID), by replacing the educational content with information intended to improve uptake of COVID19 testing and COVID19 vaccination.

2) To pilot test the intervention in Aim 1 (called LinkUP) at OnPoint's 4 mobile SSP locations across San Diego County. We expect that the LinkUP intervention will be acceptable to PWID and considered feasible and sustainable by OnPoint staff and the project's Community Scientific Advisory Board (CSAB).

7. BACKGROUND AND SIGNIFICANCE

More than one year into the pandemic, SARS-CoV-2 is becoming endemic.[1] In the US, herd immunity against this virus is increasingly being considered unachievable due to vaccine hesitancy and new circulating escape variants.[2, 3] The implications are enormous: control over COVID-19 will only become possible with vaccine equity, which requires an infrastructure to offer COVID-19 testing, vaccination, boosters and health care to the most vulnerable communities. Understanding and overcoming barriers to COVID-19 testing and vaccination and developing interventions to improve their uptake is a critical public health priority.

COVID-19 Testing and Vaccination is Lagging Among PWID. California has done an admirable job of scaling up COVID-19 vaccination. However, like the rest of the country,[4] vaccine coverage is lower among under-represented minorities, especially Blacks and Latinx.[5, 6] To date, in the parent study (La Frontera), we have found that 36% tested seropositive for COVID-19 antibody. Of note, 32% had a COVID test before they joined our study, but 65% of those testing SARSCoV-2 seropositive had not been tested previously, indicating that the 'worried well' are those seeking testing, whereas the highest risk PWID are not.[7] Further, despite a robust vaccination program in San Diego County, only 9% of La Frontera participants had received a COVID vaccine as of Sept/21 and only 55% report they were willing to be vaccinated.[8] Further, we found that beliefs in COVID19 conspiracy theories and obtaining most of their COVID19 information from social media were independently associated with vaccine hesitancy.[8]

SSPs are undergoing expansion in CA and elsewhere. Research by our team and others consistently shows that syringe exchange programs (SSPs) attract PWID who are at higher risk of acquiring HIV and HCV,[9-12] representing a 'touchpoint' for those outside the health care system. SSPs are ideally positioned to offer ancillary services, such as referrals to substance abuse treatment, overdose prevention, testing for HIV, HCV, STIs and TB, as well as HBV vaccination and PrEP.[13] Mobile SSPs can reach the most vulnerable PWID who are homeless and lack transportation.[14] Across the US, states where SSPs can operate legally are more likely to offer these services, as well as medical care,[15] but their role in prevention, testing and vaccination for COVID-19 has been under-utilized.[16] 185 SSPs operating in the US have potential as venues to reach PWID at high risk of COVID-19.[16] The CDC and CDPH publicly endorse SSPs,[17, 18] and SD County's Supervisors recently embraced SSPs in 01/21.[19] In 2020, CDPH provided funding to 37 SSPs

across the state, including our lead community partner, the SD Harm Reduction Coalition's SSP, OnPoint. The CDPH are now offering free rapid COVID-19 and confirmatory PCR tests at SSPs across CA as well as free COVID-19 vaccinations. However, medical mistrust and vaccine hesitancy are anticipated to be persistent barriers, which our intervention will address. By basing our intervention at a SSP, we will create a potential model for pandemic preparedness that could be replicated at other SSPs to improve COVID testing and vaccination, which has been deemed a priority by NASTAD.[16]

This project is significant because PWID represent a medically and socially vulnerable population. High proportions of our study participants are ethnic minorities (75%), homeless (68%), have been in jail/prison (45%) or are HIV+ (6%). Our study team is uniquely poised to adapt and pilot an appropriate intervention in partnership with our established community partner, OnPoint, to encourage uptake of COVID19 testing and vaccination among PWID. Our prospective parent study, La Frontera, offers a mechanism to follow-up outcomes among PWID who are co-enrolled in LinkUP and compare them to those who are not. If our LinkUP intervention is deemed feasible and acceptable, we plan to apply to the NIH for additional funding to test its efficacy in other SSP locations around the US.

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

La Frontera Parent Study Infrastructure: The parent study, La Frontera (R01 DA049644; PI: Strathdee; UCSD IRB #191390) was funded by NIH on 04/1/20 and is collecting prospective survey data and serology for HIV, HCV and SARS-CoV-2 on 600 PWID in both San Diego and Tijuana through 2025. This sub-study (LinkUP) will focus only on 150 PWID living in San Diego County based on the following eligibility criteria. LinkUP is funded by NIH through the RADxUP consortium, through the American Recovery Act which was enacted by US Congress in response to the COVID-19 epidemic.

Eligibility criteria for LinkUP. PWID participating in La Frontera were aged 18 or older at their baseline visit in 2020-2021, reported living in San Diego County, and injecting drugs within the last month. All were recruited into La Frontera between October 2020 and September 2021. To be eligible for the LinkUP substudy, subjects must be enrolled in La Frontera, report not having ever been tested for COVID-19 outside of La Frontera, and report not having had any vaccinations against COVID-19. They must also have provided consent to release their medical records with the study team, and consent to share their de-identified data with the RADxUP Data Coordinating Center at Duke University. Information on eligibility will be obtained through participants' most recent interviewer-administered survey in La Frontera. Potentially eligible participants who indicated that they are interested in participating will be contacted by La Frontera staff beginning March 1, 2022, at which time their eligibility for the LinkUp study will be re-confirmed using a short interview (screener) to ensure that their eligibility concerning COVID-19 testing and vaccination has not changed.

Baseline Data Collection. La Frontera staff will obtain written informed consent in person from the first 150 eligible La Frontera participants, who will form the LinkUP study sample. Consent forms will be offered in both English and in Spanish by trained bilingual staff. The LinkUP consent form will include permission to share their de-identified data between the OnPoint SSP and our study team. LinkUP participants whose last La Frontera interview was more than 3 months ago will undergo a brief interviewer-administered survey that addresses their potential barriers to COVID-19 testing and vaccination (baseline LinkUP survey). Measures include beliefs and attitudes to COVID testing and vaccination as well as structural barriers (e.g., lack of transportation, homelessness); these measures are already approved by the IRB under the parent study (IRB #191390). Surveys will be conducted by La Frontera's interviewers using computer-assisted programmable interviewing (CAPI). Interviews are done under canopies outside La Frontera's mobile van with plexiglass partitions and PPE for both interviewer and participant, as we have done for the La Frontera parent study. Interviews will be offered in both Spanish and English by trained bilingual staff. Participants will also undergo venipuncture for SARS-Co-V-2 serology. Following centrifugation, sera are batched and delivered to Genalyte

(San Diego, CA), a CLIA-certified lab that has obtained Emergency Use Authorization for their SARS-CoV-2 Maverick® Multi-Antigen Serology Panel[20] and tests for IgM and IgG antibodies against 13 unique viral antigens. Sensitivity and specificity for detecting SARS-CoV-2 antibody is 96% and 98% respectively. Following the interview and blood draw, each of the 150 participants will be given a laminated coupon indicating the address of the closest OnPoint syringe exchange location and the program's schedule and encouraged to attend this location at their earliest convenience. All enrolled participants will be provided with $20 to reimburse their time and the cost of transportation.

Cluster Randomization. The four OnPoint syringe exchange locations will be randomized to deliver either the active (intervention) or didactic (control) version of the LinkUP intervention. The randomization scheme will be developed using an algorithm by La Frontera's statistician. Approximately three months into enrollment, there will be a one-week 'washout' period, after which time the two original intervention syringe exchange sites will become control sites and the two original control sites will become intervention sites. This cluster randomization scheme will help ensure that no neighborhood in San Diego County is denied access to the LinkUP intervention. By the end of the study, 75 LinkUP participants will have been randomized to an intervention site and 75 will have been randomized to a control site.

Participant Intake and Out-take Data at OnPoint Locations. OnPoint peer counselors will confirm that their client is a LinkUP participant when they are presented with the laminated card that was provided by LinkUP staff. They will then conduct a short 5 minute interview with the participant to obtain information on their COVID testing and vaccination history, their health status and any of their harm reduction needs to facilitate any referrals. After their visit, the peer counsellor will supplement this with the Out-take data, which includes whether or not the participant received the LinkUP intervention and COVID-19 test(s). The information obtained will be shared through record linkage between OnPoint and La Frontera to confirm the study outcomes. Following the intake interview, the participant will either receive the LinkUP active or didactic intervention depending on the randomized allocation of the SSP site.

LinkUP Active intervention. The LinkUP intervention will be adapted from an intervention developed by UCSD faculty member Dr. Angela Bazzi, who developed an intervention combining education, motivational interviewing (MI), problem-solving, and ongoing support from peer navigators to increase uptake of and adherence to HIV pre-exposure prophylaxis (PrEP) among PWID attending SSPs in Massachusetts.[21, 22] The content of Dr. Bazzi's PrEP intervention will be replaced with content on COVID-19, including basic information on its biology and epidemiology, and the safety and efficacy of available COVID-19 vaccines. This information will be drawn from literature shared by our RADxUP consortium leaders and is based on that provided by the CDC. Through an open discussion with one of OnPoint's peer counselors who are trained in MI, the counselor will present evidence-based COVID-19 information, which will also address COVID-19 misinformation (e.g., that COVID is no worse than the flu), and COVID-19 disinformation (e.g., that COVID vaccines include a tracking device). Next, the counselor will attempt to identify the participant's concerns about COVID-19 and vaccination in an attempt to tip their decisional balance. For example, in in-depth interviews, some participants expressed interest in vaccine only because it protected their loved ones whereas participants who are older or who have co-morbidities like obesity, HIV or diabetes may be more willing to consider COVID-19 testing or vaccination if they realize they are at risk of more serious disease. This session will be designed to be completed within 45 minutes. The LinkUP intervention will be available in English and Spanish. Qualified bilingual, bicultural staff will translate and back translate the intervention materials into Spanish. See Table 1 below for more detailed information on the intervention.

LinkUP Control Condition (didactic intervention). Given the vulnerability of our population, we plan to offer a didactic version of the LinkUP intervention as the control condition. Like the active version of the intervention described above, the didactic component will be conducted by an OnPoint counselor. They will be instructed to answer any questions the participant may have but to not engage in MI counseling. The same educational materials used above will be used for this session and it will be completed within 45 minutes. See Table 1 below for more detailed information on the intervention.

Table 1. LinkUP Intervention Components and Example Strategies

Component	Examples of Specific Strategies	Mediators
(a) COVID-19 Testing & Vaccine Education*	• Learning about COVID-19 symptoms and testing • Debating and debunking local COVID-19 misinformation (e.g., vaccine myths) • Learning about COVID-19 vaccines (including efficacy, doses, booster Q&A) • Identifying where and how to obtain testing and vaccines	Increased COVID-19 testing & vaccine knowledge
(b) Motivational Interviewing**	• Reviewing factors contributing to local SARS-CoV-2 transmission, presenting plausible scenarios, adding personal meaning incl. personally-relevant risks • Rating personal testing and vaccine motivation; discussing what could increase it • Discussing costs and benefits of testing and becoming fully vaccinated • Elaborating on personally-relevant advantages of testing and vaccines • Aligning COVID knowledge/risk perceptions with testing and vaccine behaviors	Increased COVID-19 testing & vaccine interest & motivation
(c) Problem-Solving and Planning**	• Problem-solving around personally-relevant challenges (e.g., competing health or priorities, schedules, homelessness, and other social and structural challenges identified by participants in formative research or by stakeholders*) • Providing enactive mastery experiences (i.e., practicing new skills) • Role modeling effective discussions with peers and healthcare providers • Handling missed appointments and devising back-up plans	Increased COVID-19 testing & vaccine self-efficacy & behavioral skills
(d) Ongoing Support**	• As-needed assistance with: (i) planning/scheduling testing and vaccine appointments, (ii) attending appointments (accompanying if desired); (iii) problem solving around new/persistent challenges identified by participant; (v) maintaining cues/reminders for appointments; (vi) obtaining referrals for other health and social services • Reinforcement (verbal encouragement) for making, following-through on plans • Future planning for ongoing testing and sustained vaccination (as needed and recommended, incl. boosters), developing systems for continued reminders, identifying external social supports	Reduced structural barriers to testing & vaccination

*Given to all participants (i.e., both active and didactic LinkUP intervention arms).
**Given to only those participants assigned to a SSP site offering the active LinkUP intervention.

Both interventions will be offered in English or Spanish by trained bilingual staff.

COVID testing. The CDPH is now providing free rapid COVID-19 antigen tests (BiNaxNow®)[23] to SSPs across California, including OnPoint, This means that SSP clients can access free rapid COVID tests regardless of whether or not they are participants in the LinkUP study, as part of their standard of care.

After the participant receives either the active or didactic LinkUP intervention, the OnPoint peer counselor will offer the participant a rapid COVID antigen test, delivered on site at their SSP location. If the participant agrees to testing, it will be accompanied by brief pre- and post-test counseling according to the CDPH's training module, which is being offered to OnPoint staff in December 2021. BiNaxNow's rapid test is conducted on a nasal swab and provides results within 15 minutes. Those testing positive will be asked to provide a nasal swab for PCR confirmation at a CDPH certified lab. Participants who prefer to have a PCR test instead of a rapid test will be permitted to do so. Participants who receive PCR tests will be asked to provide their contact details to permit the counselor to contact them to receive their test results. Subjects testing positive on either or both tests will be advised to practice social distancing and when necessary, referred to available resources for homeless. Any participant testing positive or who has symptoms consistent with COVID-19 will be referred to the nearest community clinic for free medical care.

COVID-19 vaccination. The CDPH is providing free COVID-19 vaccines that have been FDA-approved (i.e., Pfizer, Moderna and Janssen) to SSPs across California. Upon completion of the intervention, OnPoint will refer participants for vaccine to nearby clinics.

Participant Reimbursement: LinkUP participants will be compensated $10 for their visit at OnPoint regardless of whether or not they choose to undergo a COVID test or receive a COVID vaccine.

Outcome Ascertainment: COVID-19 Testing & Vaccination. Outcome ascertainment will involve record linkage between La Frontera and OnPoint to determine which participants visited the SSP site they were referred to, and if they received the LinkUP intervention and COVID19 tests. Since LinkUP participants who refused COVID-19 tests at the SSPs and will have obtained COVID19 vaccination elsewhere, we will obtain these data in three ways: 1) *Self-report from La Frontera follow-up interviews* conducted 6 months after randomization. 2) *Record linkage with the CDPH's COVID-19 database* based on electronic health records (EHRs) for participants who provided a release of medical information. Record linkage will confirm if and where COVID testing was done elsewhere, if COVID-19 vaccine was administered, type, dates and # of doses, as well as hospitalizations and deaths. 3) *Biological validation* of vaccination will also be done based on COVID-19 serology conducted by Genalyte, which is being conducted as part of their follow-up visits in the parent study, La Frontera.

Analysis: Although the LinkUP trial is not powered to assess efficacy, we will conduct an intent-to-treat analysis following CONSORT guidelines[24] and register it at clinicaltrials.gov before enrolment. We will compare socio-demographics across the two study arms (intervention and control) to ensure balance, controlling for potential confounders and study location if there are significant differences. To obtain effect sizes and standard errors, percentages along with 95% CIs for those who a) had a COVID test within 6 months of the intervention and b) had ≥ one COVID shot within 6 months of intervention, respectively, will be calculated for the two study arms. To obtain Risk Ratio estimates (intervention/control), we will use a logistic regression mixed model with a) had a COVID test; and b) had ≥1 COVID shot within 6 months of intervention, respectively, as outcomes, considering intervention (active vs. didactic) as the primary fixed effect, potential covariates (e.g., age, gender, homelessness, income) and a random intercept for subject. We will also assess acceptability and feasibility of the LinkUP intervention among OnPoint investigators, staff, and clients through focus groups and CSAB meetings.

10. HUMAN SUBJECTS

Characteristics:

Inclusion Criteria:

a) *Be enrolled in La Frontera;*
b) *report not having ever been tested for COVID-19 outside of La Frontera;*
c) *not having had any vaccinations against COVID-19*
d) *Provide consent for release of medical records with the study team*
e) *Provide consent to share de-identified data with the RADxUP Data Coordinating Center at Duke University*

Exclusion Criteria:
a) *Not enrolled in La Frontera participant;*
b) *Report having been tested for COVID-19 outside of La Frontera;*
c) *Have had any vaccination against COVID-19*
d) *Do not provide consent for release of medical records with the study team*
e) *Do not provide consent to share de-identified data with the RADxUP Data Coordinating Center at Duke University*
f) *Participation in other COVID-19 trials*

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Information on potential eligibility will be obtained through their most recent interviewer-administered survey in La Frontera. Potentially eligible participants who indicated that they are interested in participating will be contacted by La Frontera staff beginning March 1, 2022, at which time their eligibility for the LinkUp study will be re-confirmed using a short interview (screener) to ensure that their eligibility concerning COVID-19 testing and vaccination has not changed.

La Frontera staff will obtain written informed consent in person from the first 150 eligible La Frontera participants, who will form the LinkUP study sample. The LinkUP consent form will include permission to share their de-identified data between the OnPoint SSP and our study team. The OnPoint IDs are generated using 1&3 letters of both first and last name, DOB, and a gender identifier M-1, F-2, Other-3. The La Frontera study collects all the information used to generate the OnPoint IDs (i.e., names, DOB, and Gender). However, to safeguard confidentiality, the record linkage will be done without using name information (i.e., only based on DOB and gender, the combination of which is unique for each LF participant).

LinkUP participants will undergo a brief interviewer-administered survey under canopies outside La Frontera's mobile van with plexiglass partitions and PPE for both interviewer and participant. This protocol has been reviewed and approved by UCSD's office of Environmental Health and Safety. Participants will also undergo venipuncture for SARS-Co-V2 serology. Following the interview and blood draw, the 150 participants will be given a laminated coupon indicating the address of one of the 4 OnPoint syringe exchange locations and the program's schedule and encouraged to attend this location at their earliest convenience. All enrolled participants will be provided with $20 to reimburse their time and the cost of transportation.

The four OnPoint syringe exchange locations will be randomized to deliver either the active (intervention) or didactic (control) version of the LinkUP intervention. Approximately three months into enrollment, there will be a one-week 'washout' period, after which time the two original intervention syringe exchange sites will become control sites and the two original control sites will become intervention sites. This cluster randomization scheme will help ensure that no neighborhood in San Diego County is denied access to the LinkUP intervention. By the end of the study, 75 LinkUP participants will have been randomized to an intervention site and 75 will have been randomized to a control site.

OnPoint peer counselors will confirm that their client is a LinkUP participant when they are presented with the laminated card that was provided by LinkUP staff. They will then conduct a short 5 minute interview with the participant to obtain information on their COVID testing and vaccination history, their health status and any of their harm reduction needs to facilitate any referrals. After their visit, the peer counsellor will supplement this

with the Out-take data, which includes whether or not the participant received the LinkUP intervention, COVID-19 test(s). The information obtained will be shared through record linkage between OnPoint and La Frontera to confirm the study outcomes including COVID-19 vaccination. Following the intake interview, the participant will either receive the LinkUP active or didactic intervention depending on the randomized allocation of the SSP site. LinkUP participants will be compensated $10 for their visit at OnPoint regardless of whether or not they choose to undergo a COVID test or receive a COVID vaccine.

12. INFORMED CONSENT

La Frontera staff will be responsible for obtaining informed consent. Eligible participants will be informed that in order to participate in the LinkUP study they need to provide consent for release of medical records with the study team, and consent to share their de-identified data with the RADxUP Data Coordinating Center at Duke University. In addition, the informed consent form will include information about the intervention and the equal probability to be assigned to either the motivational interviewing or didactic component of the intervention. The research staff who will be responsible for obtaining informed consent will assess whether the potential participant has understood the study and consent form by asking key questions (e.g., “How much time will this take you?”; “What are the possible benefits for you?”). Because it is possible that some of our participants may be cognitively impaired, or they may not initially understand the consent process, we will test all potential participants for their comprehension of critical points in the consent form. Errors will be corrected and these potential participants will then be asked if they need further clarification. If, after further attempts to clarify any misunderstandings, we determine that they may not fully comprehend the critical aspects of the study, they will not be enrolled. The field coordinator will also be available to answer any questions raised by a given participant. If a potential participant decides she or he does not wish to participate, his or her decision will be honored regardless of how well they comprehend the study information. A copy of the consent form without any identifiers will be offered to all participants. The consent form includes a description of the study, the telephone numbers of the PIs where participants can call or leave a message 24 hours a day if they have any questions or concerns.

13. ALTERNATIVES TO STUDY PARTICIPATION

If an eligible La Frontera participant refuses to be participate in LinkUP, the participant will be reassured that he/she continues participating in La Frontera. Refusals to participate in LinkUP will be considered a feasibility outcome in our intent to treat analysis. Similarly, the CDPH is providing free rapid COVID-19 antigen tests (BiNaxNow®)[23] and free COVID-19 vaccines that have been FDA-approved (i.e., Pfizer, Moderna and Janssen) to SSPs across California, including OnPoint. Therefore, access to these services would still be available to them outside of LinkUP study participation.

Counseling services and monitoring and treatment for COVID-19 are also provided at community clinics in San Diego free of charge, regardless of their health insurance status.

14. POTENTIAL RISKS

The most serious risks of the study may include loss of confidentiality. At no time will individual results or responses to questions be available to persons outside the study team and the RADxUP Data Coordinating Center. Data shared with the RADxUP Coordinating Center will not include names. Record linkage between On Point and La Frontera will be conducted using non-nominal identifiers, by La Frontera’s Data Manager (See 11. Above for more detailed information). While study forms will not contain participant’s name, there is a small chance that someone may discover that a given person participated in the LinkUP study. If this were to happen, it could affect a participant’s employability and/or insurability, as well as psychological distress, discrimination, and possible victimization. It could also include violation of privacy, or possible discomfort/distress. Further mentioned in item 15 are the procedures in place to ensure there is no access to private data beyond the research team.

Other potential risks identified include:
The most commonly expected risks of the study are discussing topics that might make participants feel uncomfortable or upset. Participants will be reminded that they can ask any of the researchers or OnPoint counselors to leave or stop talking to you at any time and participants can change their mind about agreeing to participate in LinkUP even after they have started. Participant will also be advised that if they would like to see a counselor after talking with LinkUP staff, they can arrange for that without any cost to the participant.

If a participant is are asked to provide a blood specimen because his/her last La Frontera visit was more than 3 months ago, he/she may experience a risk of bruising or discomfort during the procedure. However, every precaution will be taken to reduce the risk of the blood draw as our staff is well trained and has extensive experience. Participant will be asked to provide 5-10 cc blood sample (1-2 teaspoons) for testing. To date, there have been no reports of participant bruising or discomfort during this procedure by our phlebotomists.

Risk of SARSCoV-2 community transmission on study premises: It is possible that community transmission could take place on the study premises while interviewers/counselors are interacting with study participants. We will make every attempt to implement control measures: potential participants will be given a face protection device upon entering the premises to be worn at all times while on the study premises and will be requested to wash their hands with soap and water or with hand sanitizer; next, participants will be screened in the open air in the area designated for this purpose with plenty of air flow; only two participants will be seen at a given time by study staff: one completing the symptom screening questionnaire while the second one is undergoing biological sample collection and testing; both stations will be placed at least 15 feet apart to guarantee social distancing at all times. Study staff will wear face protection, N95 masks, nitrile gloves at all times and any other protective equipment deemed necessary. We will also setup clear, plastic screens to provide a physical barrier between study participant and study staff while completing the supplemental survey. Upon completion of all study measures, study participants will be given an extra facial protection and useful information about SARSCoV-2 preventive measures and led to the facility's exit area. We have developed a detailed protocol based on CDC Guidelines for SARSCoV-2 screening in community settings. To date, over the 24 month period that the parent study has been collecting data using this protocol, there have been no instances of SARSCoV-2 community transmission on study premises. This protocol has been reviewed and approved by UCSD's office of Environmental Health and Safety.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Confidentiality of participation:
Every possible procedure to prevent breach of confidentiality will be taken to ensure there is no access to private data beyond the research team. Dr Strathdee in over two decades has never experienced a negative incident with respect to loss of privacy, confidentiality, victimization or psychological distress. We will apply for a Federal Certificate of Confidentiality that will allow us to protect participant information from outside requests and subpoenas in the U.S.

All study staff will be trained not to press participants to answer questions or address issues that seem to be distressing to them, and intervention will be terminated if the participant is overly distressed, fatigued, or frustrated by the effort. In the event that clinically significant depression symptoms, suicidality, or other psychiatric conditions are noted, the staff will be instructed to report any incidents or concerns to the field coordinator who will arrange for appropriate referral to available mental health referrals in the community.

In addition, the PI, all co-investigators, all field study staff and ONPoint counselors will have completed Human Subjects Training and CITI Certification Program before data collection begins.

Participant Withdrawal from Study:
At any time during study participation, staff will carefully minimize calling undue attention to participants to maintain their confidentiality and clearly advising them that they may ask the staff to leave/discontinue the conversation/interview at any time if they wish so. Participants' wishes and concerns will always be immediately respected. Similarly, participants are reminded they have an option not to participate and that there are no consequences for not participating.

Communication with Local Authorities
A signed letter from the principal investigator outlining the study objectives and duration will be sent to San Diego police department. Heightening awareness and ensuring support from local police authorities will not only increase safety for participants and study personnel, but will also reassure study participants that their involvement in the study will in no way put them in any danger or lead to harassment by the police.

We will implement SARSCoV-2 transmission control measures following CDC Guidelines for healthcare settings adapted to our study site: potential participants will be given a face protection device upon entering the premises to be worn at all times while on the study premises and will be requested to wash their hands with soap and water or with hand sanitizer; next, participants will be screened in the open air in the area designated for this purpose with plenty of air flow; only two participants will be seen at a given time by study staff: one completing the symptom screening questionnaire while the second one is undergoing biological sample collection and testing; both stations will be placed at least 15 feet apart to guarantee social distancing at all times. Study staff will wear face protection, N95 masks, nitrile gloves at all times and any other protective equipment deemed necessary. We will also setup clear, plastic screens to provide a physical barrier between study participant and study staff while completing the supplemental survey. Upon completion of all study measures, study participants will be given an extra facial protection and useful information about SARSCoV-2 preventive measures and led to the facility's exit area. We have developed a detailed protocol based on CDC Guidelines for SARSCoV-2 screening in community settings.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Our committee structure ensures smooth data collection and communication between UCSD and OnPoint, the RADxUP consortium and CDCC. Our Steering Committee will be co-chaired by Dr. Strathdee and Stamos-Buesig and will consist of Drs. Patterson and Davey Smith (both Co-Is), and Ms. Abramovitz (Senior Statistician). It will meet monthly to review progress towards project milestones, recruitment and follow-up, progress reports to CDCC and NIH, manuscripts and dissemination plans and will review potential interventions to propose.

Our Community and Scientific Advisory Board (CSAB) is comprised of 10 community stakeholders and scientists not directly involved in LinkUP, at least one of whom has lived experience as PWID. It began meeting monthly in Sept 30/21 to review preliminary results from Aim 1 and 2, and recommended the appropriate intervention to adapt for LinkUP. Scientists include ***Peter Davidson, PhD*** a harm reduction researcher and UCSD faculty; ***Laramie Smith***, ***PhD*** a Latinx social psychologist and UCSD faculty. Community stakeholders include ***Matt Curtis,*** from the CDPH, ***Winston Tilghman, MD*** from the SDHHS, ***Fatima Munoz, MD, MPH***, VP of Research at San Ysidro Health Clinic, ***Lisa Sylvestro, RN*** a nurse-practitioner at Family Health Centers and ***Kirin Macapuguay***, community organizer and founder of Asian Pacific Islander Community Actions. To facilitate cross-site comparisons, we will also include two RADxUP collaborators, ***Heather Bradley, PhD*** from Georgia State University who is studying barriers to COVID testing

among African Americans, and psychologist ***Camille Cioffi***, ***PhD*** from the University of Oregon. We also include a current OnPoint client, ***Annie*** (last name omitted to protect confidentiality).

Our Consortium Data Reporting Unit (CDRU) will be co-chaired by Dr. Patterson and Ms. Abramovitz and will also include a dedicated full-time data manager, Ms. Artamanova who has worked with our team for >10 yrs, along with Ms. Christensen from OnPoint. CDRU team members will work closely with the RADx^{SM}-UP CDCC to harmonize measures and ensure that data are collected and transferred smoothly, adhering to data security protocols. Unit members will also participate in CDCC-organized activities, including monthly cross-site meetings, cross-site working groups, and dissemination activities to share effective implementation strategies, tools and measures. Our semi-annual progress reports will include testing results, barriers and facilitators of COVID-19 testing and vaccination, key milestones and challenges to LinkUP implementation.

Our Human Subjects Unit (HSU) will monitor ethical and social implications or potential concerns and will be co-chaired by Dr. Davey Smith and Ms. Christensen. It will also include Dr. Strathdee and Mr. Vera (La Frontera project coordinator). Adverse events will be reported to the HSU and if deemed appropriate, to UCSD's Human Research Protection Program, DSMB, NIH and CDCC (refer to Data Safety and Monitoring Plan for details on the DSMB membership and activities).

17. POTENTIAL BENEFITS

Benefits to the subject include free confidential testing and counseling for SARASCoV-2, as well as linkage to OnPoint SSP services, and referrals for COVID-19 vaccination and facilitated referrals for medical/social care, in a population that has traditionally been medically underserved. Vaccinations will generate reductions in COVID-19 disease transmission in San Diego which will improve general public health. The testing of participants to determine SARS CoV-2 serostatus at follow up visit will potentially lead to early identification and early treatment of SARS CoV-2. In addition, voluntary SARS CoV-2 testing and counseling has been shown to generate reductions in disease transmission in the community. Added benefits include learning more about COVID-19, demystifying myths surrounding COVID, how to access testing and vaccination and possibly, increased individual knowledge may carry some general public health benefit consequently.

18. RISK/BENEFIT RATIO

The direct benefits that subjects can derive from participating in the study are: a) obtaining evidence-based information on SARSCoV-2 transmission, and testing; b) obtaining results of testing for SARS-CoV-2; b) obtaining information on disease transmission, treatment, and protection from infection; c) information about drug treatment programs in their local community; d) respectful companionship and advocacy for emergency and supportive services by counselors, epidemiologic survey administrators and outreach personnel. Potential significant risks associated with the research are breach of confidentiality about study participation or personal information collected in the intervention forms, interview, and testing. Since steps are taken by the researchers to mitigate the probability of the occurrence of these risks, we feel that the potential benefits outweigh the potential risks identified.

19. EXPENSE TO PARTICIPANT

None other than time taken and, depending on where they live and work, transportation to the clinic.

20. COMPENSATION FOR PARTICIPATION

Quantitative Questionnaire Reimbursement: If a participant joins the LinkUP study and completed their last parent study visit more than 3 months ago, subjects will receive $20 for their LinkUP interview. Participants will also receive $10 for their visit to OnPoint. In total, they can receive up to $30 dollars in compensation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Steffanie Strathdee, Ph.D (PI) an epidemiologist with >20 years' experience and >650 publications on HIV prevention research among PWID, including vaccine studies.[25-28] She was supported through a NIDA MERIT Award through May 2021, and was Co-I on the STAHR PWID studies in SD. She has led SSP evaluations in Canada, the US and Mexico including a case management intervention based at the Baltimore SSP that successfully linked PWID to drug treatment.[29] She is also the PI of La Frontera.

Thomas Patterson, PhD - Co-Investigator, Distinguished Professor, is an HIV prevention scientist with 20 years' research on behavioral interventions to reduce risky behaviors among substance users, especially using motivational interviewing (MI).

Davey Smith, MD – Co-Investigator, is an infectious disease physician and director of the Antiviral Research Center Lab (AVRC), who is overseeing national COVID-19 vaccine trials and therapeutics through the ACTIV-2 adaptive trial.

Angela Bazzi, PhD, MPH – Co-Investigator, is an Associate Professor in the Herbert Wertheim School of Public Health at University of California, San Diego, who has been conducting PrEP intervention research with PWID for >7 years. Dr. Bazzi developed an intervention combing education, motivational interviewing (MI), problem solving, and peer navigator support to increase uptake of and adherence to PrEP among PWID attending SSPs in Massachusetts. The content of Dr. Bazzi's PrEP intervention will be replaced with content on COVID-19, including basic information on its biology and epidemiology, and the safety and efficacy of available COVID-19 vaccines. Dr Bazzi will work closely with Drs. Strathdee and Patterson on the adaptation of the content of the LinkUP intervention.

Tara Stamos-Buesig – Subconsortium PI, a harm reduction specialist with training in MI and case management, director of OnPoint, established in 2018, member of the Harm Reduction Coalition of SD (HRCSD). As the only mobile, needs-based SSP in SD County, OnPoint provides harm reduction services including safer injecting, smoking and safer sex supplies, naloxone and fentanyl test strips. In 2020, they served >1100 clients and attract ~100 new clients each month.

Ann Christensen, ***MHS – Subconsortium Co-Investigator,*** is a health care administration expert who has worked with OnPoint since its inception

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Alicia Harvey-Vera, MPH, PhD – Project Director. Dr Vera is fully bilingual and bicultural with an MPH and PhD from the Universidad Autonoma de Baja California. She has directed our research projects on both sides of the San Diego/Tijuana border for 15 years. She has expertise in both qualitative and quantitative data collection with marginalized populations. She will supervise the team's field work in quantitative survey data collection. She will be responsible for the training of interviewers and outreach workers together with Drs. Strathdee and Ms. Stamos; piloting and revising the study instruments; creating protocols for maintaining all study-related documents; overseeing subject screening, interviewing, follow-up and daily data transfer; preparing and maintaining human subjects protocols in the U.S. and liaising with co-investigators, field staff and policy makers.

Carlos Vera, MPH - Project Coordinator. Dr Vera is fully bilingual and bicultural with an MPH from the Universidad Autonoma de Baja California and is also a trained and certified phlebotomist. He has expertise in quantitative data collection with marginalized populations as well as clinical trials. He is the project coordinator for the parent study (La Frontera) and will supervise the team's quantitative survey data collection for LinkUP,

randomization of the subset of participants (N=150) who agree to be recruited into LinkUP, and their follow-up (which is conducted as part of La Frontera). He will also translate protocol materials into Spanish and assist in the training of peer counselors to deliver the LinkUp intervention together with Drs. Strathdee and Ms. Buesig-Stamos; piloting and revising the study instruments; creating protocols for maintaining all study-related documents; overseeing subject screening, interviewing, follow-up and daily data transfer to Ms. Artamanova at the data center; preparing and maintaining human subjects protocols and liaising with co-investigators and field staff.

Daniela Abramovitz, M.Sc – Senior statistician. Ms. Abramovitz is a biostatistician who completed all the course requirements for a PhD in biostatistics. She has >15 years' experience in data management and analysis and joined our UCSD research team in 2005. She has overseen analyses for all of our San Diego and Tijuana studies, and is also well versed in statistical techniques for prospective cohort studies and intervention studies, including random effects models, Cox regression, Poisson regression, hierarchical modeling techniques and mediation analyses. She will oversee Ms. Artamonova's data management and programming of the baseline and follow-up surveys in QDS.

Irina Artamonova, MS. – Quantitative Data Manager. Ms. Artamonova is a data manager who has worked for our binational research team for 7 years. She will be responsible for programming the baseline and follow-up surveys in QDS to allow the interviews to be conducted using CAPI. She will also monitor the transfer of data collected at the mobile sites and will concatenate data from each timepoint into the study's central database. She will develop a system for tracking participants' visits and keeping complete records, organizing and filing data, and storing consent forms. She will also generate summary data reports and conduct basic statistical analyses under the supervision of Ms. Abramovitz.

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23. FUNDING SUPPORT FOR THIS STUDY

The main study is funded by the National Institutes of Health (NIH) – National Institute of Drug Abuse (NIDA) (R01 DA049644). The grant's project period is from 04/01/2020 until 01/31/2025. This project is also funded by a competitive revision through the RADxUP program, which itself is funded by the American Recovery Act under a congressional mandate. The RADxUP project period is from 09/01/2021-08/31/2023.The fiscal contact person for both of these projects is Mr. William Gentz wgentz@health.ucsd.edu.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Transfer protocols will be worked out between field staff in Tijuana, field staff in San Diego, and the UCSD CFAR laboratory, Genalyte Laboratory, and CDC Laboratory to ensure the safe storage and timely testing of biosamples.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON NURSING STAFF

Not applicable.

27. CONFLICT OF INTEREST

The researchers involved in the study do not have any conflict of interest.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

The research staff who will be responsible for obtaining informed consent will assess whether the potential participant has understood the study and consent form by asking key questions (e.g., "How much time will this take you?"; "What are the possible benefits for you?"). Because it is possible that some of our participants may be cognitively impaired, or they may not initially understand the consent process, we will test all potential participants for their comprehension of critical points in the consent form. Errors will be corrected and these potential participants will then be asked if they need further clarification. If, after further attempts to clarify any misunderstandings, we determine that they may not fully comprehend the critical aspects of the study, they will not be enrolled. If a potential participant decides she or he does not wish to participate, his or her decision will be honored regardless of how well they comprehend the study information.