NCT04418076 Study Protocol and SAP
Date: April 13, 2020
Title: Improving Antiretroviral Adherence and Persistence Using mHealth Tools in HIV-infected Cocaine Users

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research

100 FR1 (2015-1)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Improving Antiretroviral Adherence and Persistence using mHealth Tools in HIV-infected Cocaine Users			
Principal Investigator: Frederick L. Altice		**Yale Academic Appointment:** Professor of Medicine, Epidemiology and Public Health	
Department: Internal Medicine, Section of Infectious Diseases, AIDS Program			
Campus Address: 135 College Street, New Haven, CT 06510			
Campus Phone: 203-737-2883	**Fax:** 203-737-4051	**Pager:**	**E-mail:** Frederick.altice@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Xin Zhou, 135 College Street, New Haven, CT 06519			
Campus Phone: 781-266-7983	**Fax:**	**E-mail:** xin.zhou19@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research http://www.yale.edu/hrpp/policies/index.html#COI

❑ Yes X No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

❑ Yes X No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus
☒ Specify Other Yale Location: 270 Congress Ave, New Haven; and 330 Main Street, 3rd Floor, Hartford, CT 06106

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven

☐ Other Locations, Specify:

☐ International Research Site
(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. Aug.1, 2016 – July 31, 2018

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☒ Clinical Research: Outcomes and Health Services
☒ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☐

Other (*Specify*)

The proposed study includes a randomized, pilot feasibility trial that may require registration at ClinicalTrials.gov. If funded, the Principal Investigator agrees to register the proposed study as required. All currently funded studies by the Principal Investigator are currently registered at this site and are identified within the respective publications.

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
   Yes ☐ No☐ n/a

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No _X__ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

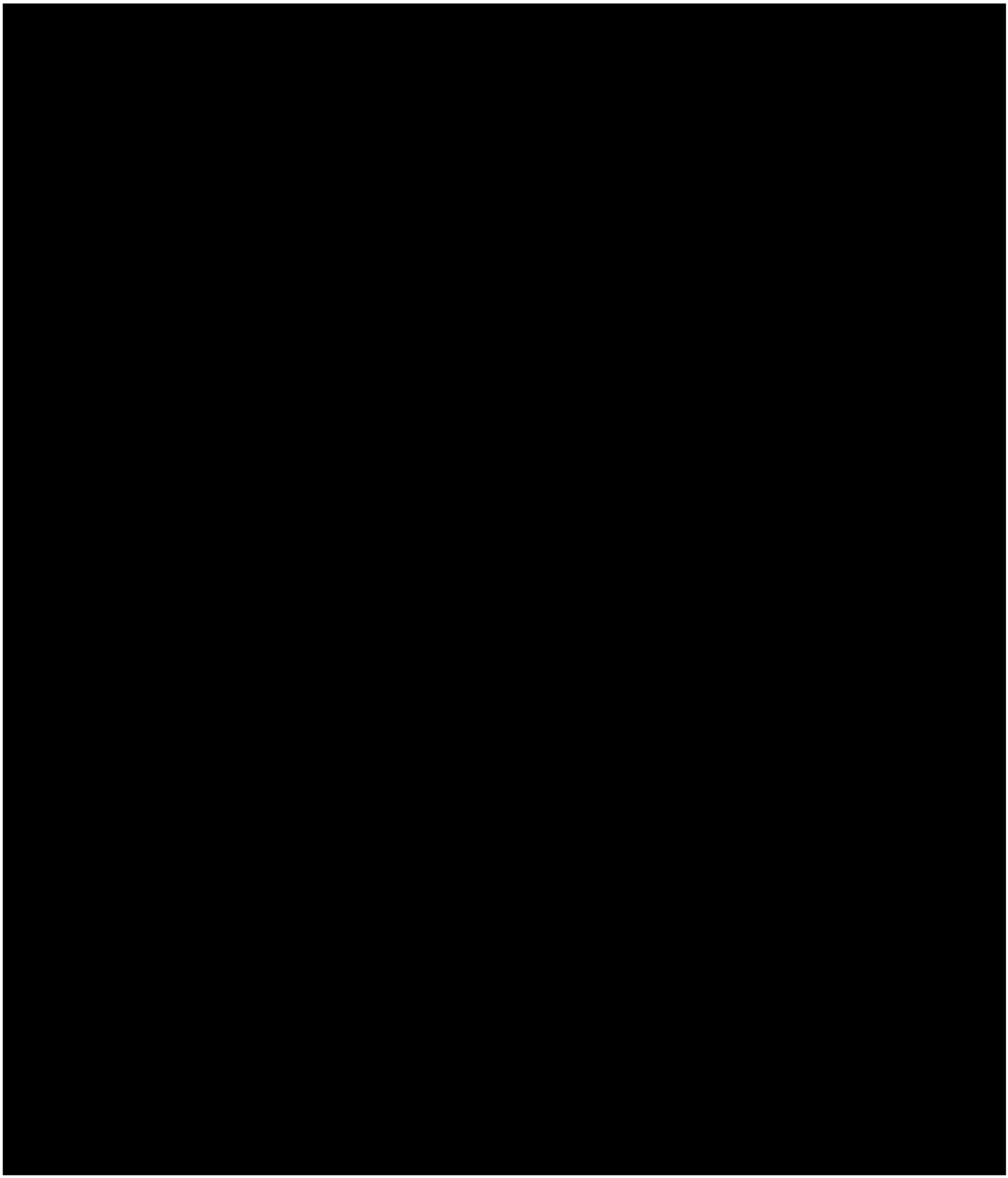
SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

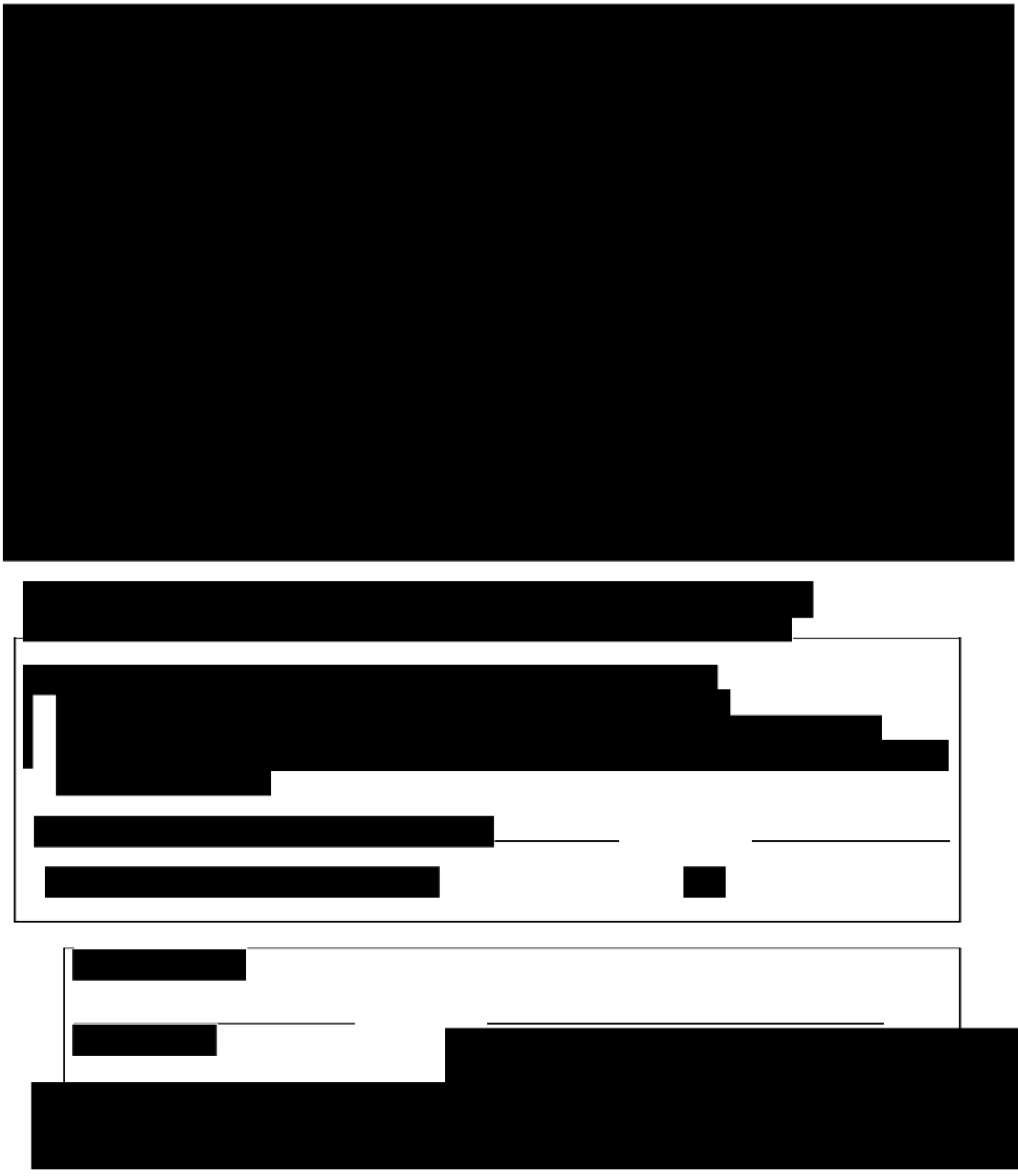
1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply.
   Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

[redacted]

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.





1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   The aim of this study is to examine the effect of mHealth tools on antiretroviral (ART) adherence and persistence among HIV-infected individuals with co-occurring cocaine use disorders (CUDs). The specific aims are:

   (1) To conduct qualitative assessments using focus groups of people living with HIV (PLH) who use cocaine and healthcare providers that will assess the acceptability, feasibility, facilitators and barriers of implementing mHealth interventions; and will aid in developing the final design and content of both automated and clinician feedback in preparation for designing a pilot feasibility study.
   (2) To conduct a 12-week pilot feasibility RCT among PLH with co-occurring CUDs that will examine the impact of mHealth tools (cellular-enabled smart pill boxes and cell phones) and feedback (no feedback vs. automated feedback vs. automated + clinician feedback vs. vs. automated + text-reminder from a social network) on primary (ART adherence and persistence) and secondary outcomes (HIV viral suppression, cocaine use, retention in HIV care).

   The hypotheses include:

   (1) Patients with automated feedback + clinician feedback will have higher ART adherence and persistence than patients with only automated feedback and patients with no feedback.
   (2) Patients with automated feedback + clinician feedback will have improved HIV outcomes including lower changes in log10 HIV-1 RNA levels, higher CD4 counts and higher rates of retention in care, compared to patients with only automated feedback and patients with no feedback.
   (3) Patients with automated feedback + clinician feedback will have decreased cocaine use compared to patients with only automated feedback and patients with no feedback.
   (4) Patients with automated feedback + text-reminder from a social network will have higher ART adherence and persistence than patients with only automated feedback and patients with no feedback.
   (5) Patients with automated feedback + text-reminder from a social network will have improved HIV outcomes including lower changes in log10 HIV-1 RNA levels, higher CD4 counts and higher rates of retention in care, compared to patients with only automated feedback and patients with no feedback.
   (6) Patients with automated feedback + text-reminder from a social network will have decreased cocaine use compared to patients with only automated feedback and patients with no feedback.
   (7) There is statistically significant difference between a patient's ART adherence and persistence and HIV outcomes when their designated social network member lives inside vs outside patient's activity space.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Antiretroviral therapy (ART) is extremely effective at reducing morbidity and mortality, and reducing HIV transmission among people living with HIV (PLH).[1,2] Clinical effectiveness, however, is largely dependent on patients' ART adherence and persistence.[3-9] ART non-adherence and non-persistence substantially reduce viral suppression (VS)[10] and increase HIV transmission risk to others.[11-15] Substance use disorders (SUDs) further contribute to poor health outcomes, primarily by reducing ART adherence and persistence.[16-20] Cocaine use disorders (CUDs), in particular, result in a number of poor HIV treatment outcomes, including decreased retention in care, poor ART adherence and persistence, low VS, and accelerated HIV progression.[21-28] Considering the high prevalence of CUDs among PLH[29-34] and the absence of effective medication-assisted therapies (MAT) for treating CUDs, innovative strategies of improving ART adherence in this group are urgently needed.

Opioid agonist treatments for opioid dependent PLH is an effective evidence-based adherence strategy;[35,36] however, for PLH with CUDs, currently the only effective adherence intervention is directly administered antiretroviral therapy (DAART)[36] which is expensive and labor-intensive. Recent international guidelines suggest that the next generation of adherence interventions will need to be scaled back both in terms of cost and personnel.[36] Mobile health (mHealth) technologies such as cell phones can provide innovative, efficacious and cost-effective strategies to improve ART adherence and optimize HIV treatment outcomes.[37,38] They already show great promise in resource-limited settings due to their low costs and ubiquitous nature,[38-41] making their use in underserved communities such as PLH with co-occurring CUDs, particularly appealing. mHealth tools can not only monitor medication adherence in real-time (such as cellular-enabled smart pill boxes),[42,43] but can also be used to promote adherence in temporal proximity to actual medication intake through the use of automated reminders, feedback and interactive communication.[44-48] Already, text messaging using cell phones has been shown to increase treatment adherence and retention in care among patients with various chronic conditions such as diabetes,[49-53] tuberculosis,[54-56] malaria,[57-59] asthma,[47,60] and HIV,[46,61,62] but has never been developed or tested in PLH with CUDs – a highly prevalent group of PLH with problematic ART adherence and persistence.

mHealth interventions can be valuable for PLH since they make it possible to have a tightly woven network of coordinated care by providing real-time data about dosing reminders,[63,64] medication intake,[44,46] and solicitation of care.[62] The inclusion of tailored automated feedback has been especially successful at promoting positive health outcomes for other conditions,[65-67] yet has not been compared to personalized clinician feedback. Despite their immense potential, the acceptability, feasibility and effectiveness of mHealth tools have not yet been developed and tested among PLH with co-occurring CUDs. Moreover, mHealth interventions have not optimized the integration of feedback to determine what type of feedback improves outcomes. Thus, this study will provide crucial preliminary information necessary to determine acceptability, study design and implementation procedures for conducting the most optimal RCT using a quadruple (patient-mHealth-clinician-social network) relationship for improving ART adherence and persistence in PLH with CUDs.

Significance

A. **<u>ART Access, Adherence and Persistence</u>:** Among the ~1.2 million PLH in the U.S., ART adherence and persistence is problematic for many, resulting in too few patients achieving VS. In the absence of VS, HIV transmission and mortality among PLH increase.[1,2,68] Virological

failure, either through suboptimal adherence (not taking ART as prescribed)[36,69,70] or non-persistence (gaps in continuous ART treatment),[18,71] results in development of resistance mutations, increased mortality[72], and complicated care.[3-9,16-19,73] For PLH with co-occurring SUDs, there are additional negative health outcomes; active drug use is associated with clinicians not prescribing or delaying prescribing ART.[74] When ART is optimized, it also improves outcomes for other co-morbid conditions.[17] A meta-analysis has documented that patients with SUDs who receive adherence support, adhere to ART similarly to non-drug users.[75] Adherence support, however, must be provided using a strong theoretical model with documented effectiveness and in this case, be effective with SUDs.

B. <u>Negative Consequences of Cocaine Use on HIV Outcomes</u>: Although SUDs are associated with negative health outcomes; CUDs are especially problematic for access and retention in HIV care.[76-78] Cocaine use is associated with high rates of psychiatric disorders, criminal activity, negative social interactions, and risky sex practices that place users at even more risk of HIV transmission.[11-15,79] Moreover, compared to PLH with other SUDs, those with CUDs are less likely to be prescribed ART,[78,80] have problematic adherence,[22-27] and don't achieve VS,[21,30] thus resulting in accelerated HIV progression and opportunistic conditions.[28,81,82] These cumulative negative effects ultimately are responsible for AIDS-related death being 3-fold higher in CUDs than among non-drug users.[30]

C. **<u>Current ART Adherence Strategies in PLH and SUDs</u>:** The CDC supports only 10 interventions to promote ART adherence. A systematic review[35] and international guidelines only support 3 ART adherence interventions for PLH and SUDs: 1) DAART, 2) medication-assisted therapies (MAT) to treat addiction, and 3) integrated care.[16,83-85] Since CUDs are not amenable to MAT, behavioral interventions remain crucial. Even in patients on MAT and receiving DAART, cocaine reduces adherence.[86] DAART is effective irrespective of cocaine use,[19,87-89] but is rarely available and too expensive for most settings.[90] While integrated care is also effective,[35,91-98] recent international guidelines[36] suggest that the next generation of adherence interventions must be scaled back in terms of cost and personnel and incorporate three crucial "C" elements: **<u>C</u>**onvenience, **<u>C</u>**onfidentiality and **<u>C</u>**ost-effectiveness. None of the available interventions specifically address the 4th **<u>C</u>: <u>C</u>**ocaine Users. Current behavioral and structural interventions designed to reduce cocaine use have met with limited success – *interventions that support ART adherence even in the presence of ongoing cocaine use are crucial*. A RCT of a family-based structural vs. psycho-educational intervention in cocaine-using PLH found neither reduction in cocaine use nor improvement in ART adherence.[99] One pilot RCT (N=56) comparing the effects of extended, multi-session adherence counseling intervention versus a single video-based control group showed reduction in cocaine use and improvement in ART adherence over time, but without differences between groups.[100] The use of reminders linked to medication-taking, which has documented benefits,[101] was not included, but this still provides support for technology-based ART adherence improvements in HIV+ cocaine users.

D. **<u>mHealth as an Innovative and Effective Tool</u>:** In healthcare management, the use of mHealth is viewed as an innovative tool in managing personal healthcare and promoting preventive and treatment behaviors.[38,50,102,103] mHealth satisfies recommendations that newer adherence strategies be scaled back in terms of cost and personnel. mHealth interventions have already been shown to be efficacious in improving treatment adherence in patients with various chronic conditions such as diabetes,[49-53] tuberculosis,[54-56] malaria,[57-59] and asthma[47,60] and are positioned to provide efficacious and cost-effective ART adherence strategies to optimize HIV

treatment outcomes.[37,38] A 2014 meta-analysis of text messaging interventions in PLH summarized that reminders and feedback in the form of text messages improved ART adherence, with larger adherence and VS effects seen when text messages were: 1) less frequent, 2) bidirectional, 3) personalized messages, and 4) matched to dosing schedule;[104] none of the 9 studies in the meta-analysis however, sampled PLH with SUDs. New WHO guidelines now strongly recommend texting to promote adherence and retention.[101] Mobile phones and devices offer multiple benefits to PLH; they are cost-effective, require minimal direct supervision, allow flexible reminders and content and can be disseminated ubiquitously.[38,41,48,63] Three-fourths of PLH have positive perceptions regarding the use of cell phones to support their adherence behaviors.[105]. In our current NIH study (R01 HD075630) of PLH with SUDs - several with unstable housing, we have found high acceptability and retention among 48 patients video-recording their medication-taking to measure adherence. Use of mHealth tools in cocaine users remains limited to assessing drug craving and use, and only in patients without HIV.[106-108] Despite evidence that adding mHealth tools to brief interventions may be feasible and cost-effective in improving HIV outcomes in PLH and SUDs, mHealth assessments or interventions have never specifically targeted PLH with co-occurring CUDs – a remarkably vulnerable population with excessive health disparities. Developing effective adherence tools for patients with CUDs will benefit patients and encourage clinicians to not withhold ART prescription, and thus promote health strategies to treat and retain patients on ART.

Innovation: Significance and innovation are high because of the combination of several factors – (1) the focus on PLH with CUDs to promote ART adherence; (2) incorporation of qualitative assessment using focus groups among HIV+ cocaine users to examine their willingness to incorporate mHealth interventions and among healthcare providers in order to understand their interest in deploying mHealth ART interventions for patients with CUDs; , and among selected social network members to understand their interest in becoming 'health-buddy' and providing long-term and sustainable support for healthcare; (3) the intervention to be developed and pilot-tested involves two mHealth-based **reminders** (via cellular-enabled smart pill boxes and cell phones), and three types of **feedback** (automated electronic feedback based on adherence from smart pill boxes, and clinician feedback based on a weekly smartphone-based survey and weekly text-reminder from a designated social network member) – each of which has separately shown to improve ART adherence, persistence and VS in PLH but not in drug users; . In addition, prior studies have used network-driven interventions for HIV prevention but not for ART adherence, persistence, and VS in PLH and definitely not by combining mhealth tools with social relations (4) the comparison of automated electronic and personalized clinician and text-reminder from a social network member feedback as part of the intervention, especially since feedback and communication loops have been under-utilized in interventions in PLH with SUDs;[109,110] (5) extension of our established use of feedback using the Information-Motivation-Behavioral Skills (IMB) conceptual framework for adherence using a computer interface (LifeWindows project),[111] but now applied to mHealth to promote adherence; and (6) a multidisciplinary group of researchers experienced in addiction medicine, HIV, intervention development particularly adherence interventions, behavioral science, Geographic Information System (GIS), social network analysis (SNA) and mHealth who have already created CDC-recommended ART adherence interventions for drug users. Thus, this

study is uniquely positioned to provide crucial information necessary to develop a mHealth tool-enabled intervention strategy for PLH and CUDs.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   There are two specific aims within this study. In the first specific aim, we will conduct four focus groups of people living with HIV (PLH) with co-occurring cocaine use disorders (CUDs), and two focus groups of healthcare providers to assess the acceptability, feasibility, facilitators and barriers of implementing mHealth interventions. In the second aim of the study, we will conduct a pilot feasibility RCT among PLH with co-occurring CUDs to examine the effect of mHealth tools (blister pack and cell phones) and feedback loops (no feedback vs. automated feedback vs. automated + clinician feedback vs. automated + text-reminder from a designated social network member) to assess improvement in antiretroviral (ART) adherence and persistence and other HIV health outcomes.

Specific Aim 1: ***To conduct qualitative assessments using focus groups (FGs), among HIV+ cocaine users and among healthcare providers, that will assess the acceptability, feasibility, facilitators and barriers of implementing mHealth interventions; and will aid in developing the final design and content of both automated and clinician feedback in preparation for designing a pilot feasibility study.***

An initial set of 4 focus groups (FGs) comprised of 6-8 persons with HIV+ cocaine users and lasting one hour each will be conducted. Recruitment, screening, enrollment and other procedures for these FGs are discussed below. A second set of two FGs will be conducted among healthcare providers including physicians, nurses, clinic supervisors, and substance abuse counselors from HIV clinics.

Eligibility Criteria for Focus Groups of HIV-infected Cocaine Users:

- Age ≥18 years old
- HIV+
- Current cocaine use (in the past 30 days)
- Able to speak English or Spanish
- Able to provide informed consent

Eligibility Criteria for Focus Groups of Healthcare Providers:

- Currently employed as community-based HIV physician, clinician, healthcare worker, clinic supervisor or substance abuse counselor
- Speaks English or Spanish
- Able to give informed consent

I.A. Recruitment: In order to recruit people for the first four FGs of people with HIV+ cocaine users, IRB-approved flyers containing a toll-free number will be posted in a number of clinical and community venues including HIV and drug treatment clinics, our mobile medical unit, and community support groups. Due to our continued presence in New Haven through the implementation of several treatment programs and clinical trials, we are confident of being able to recruit participants for the FGs. For the FGs with healthcare providers, IRB-approved flyers containing a toll-free number will be posted in the offices of all five HIV clinics in the Ryan White Consortium. Providers from all sites have been successfully recruited and participated in previous FGs. We will also recruit through announcements in the electronic newsletter "Did You Know?" – an electronic newsletter managed by Karina Danvers, Director of the New England AIDS Education and Training Center - Local Performance Site - that is disseminated regularly to New Haven-area clinics. Letters of support from the Ryan White Consortium and the New England AIDS Education and Training Center are attached to this application.

I.B. Screening: All flyers and recruitment information will have our toll-free number. Interested individuals who call will be asked a number of questions including (a) age, (b) gender, (c) race/ethnicity, (d) HIV status, and (e) cocaine use in the past 30 days. Individuals who meet the eligibility criteria will be invited to learn more about the qualitative interviews. At that point, we will ask for a name (preferably a PSEUDONYM) that they would like to use during the FGs. We will do this so that we can make nametags that will be used to identify speakers during the FGs. Individuals who do not meet criteria will be thanked for their time and asked for permission to maintain their information in our database should the opportunity to participate in other studies arise. They will not, however, be told why they did not qualify for participation. NO specific screening will occur for the community-based clinicians and healthcare providers other than a request to provide proof of identity to verify their designations.

Enrollment: Individuals who screen positive for the first set of FGs as described above will be told more about the details of the study, including that the FGs will be conducted in a confidential setting. During these FGs, they will be told that they do not need to provide their real name and that the information will be recorded but will also be confidential. No names or other identifiers will be recorded. They will be told that we will provide certain rules that include raising their hand to speak, being identified by a pseudonym if wanted, that others within the group should be considerate of others, and reminded that the FG will be recorded. They will be given a TIME and LOCATION of the FGs and asked to show up 15 minutes beforehand to review a fact sheet and the focus group guides and provide verbal consent. Verbal consent will be used to AVOID the use of real names and minimize risk of breaches of confidentiality. These interviews will not be video recorded, and they can use a pseudonym if they do not want to use their actual names for the focus group interviews.

I.C. Procedure: Before the FGs begin, the participants will be verbally consented and be asked to review the IRB-approved information sheet that will include a description of the study, risks, benefits, privacy, and alternatives. By using the verbal consent process, we will protect the identity of the participants; no additional personal information will be collected at any point. They will be reminded that they can use fake names during the interview. Each participant will be given a nametag to use their fake name to identify each speaker in the FG and will be given a pen and

paper. The facilitator (Dr. Shan-Estelle Brown under the supervision of Dr. Altice) will begin the FG with a brief introduction including a description of the purpose of the FG; review rules of the group (e.g. turn off cell phones, protect each other's confidentiality, respect other's opinions, and speak one at a time); ensure there are no questions; and remind participants that they will be audio-recorded. FG guides will detail the conduct during and after the interview, including not using names, not discussing specific illegal activities, and maintaining the confidentiality of focus group participants. Drafts of guides for both sets of FGs are attached to this application. A note-taker will also be in the room to record non-verbal communication during the FGs. After informed consent, Dr. Brown will audio-record the sessions.

Procedure for participants affected by technical problem with the pillbox: Due to a technical error with the pillbox, real time adherence data of 8 participants were not collected from July 19, 2018, and they also were not able to receive the interactive text reminders to take medication. This has caused us to lose up to a month's adherence data from the boxes. The following actions will be taken to resolve and move forward with the study:

- We will extend participation by one month (4 weeks) to the end date so that the 8 participants end up receiving all 12 weeks of intervention. Since participants will be at different stages (because of rolling recruitment), we will accordingly adjust the timeline for each participant. Hence, 8 participants will be participating in the study for about one month longer than the original time-line of the study.

Transcription and Analysis of Data: The audio files from all of the FGs will be sent to a licensed HIPAA-compliant professional transcription service using secure and encrypted transfer systems. After transcription, audio recordings of the FG discussions will be first locked in double protected cabinets and destroyed after verification of the information. After transcription of all FGs, content analysis – a technique designed to uncover meaningful patterns and themes. Transcribed text will be coded into themes using an iterative process. The text will first be reviewed in a preliminary review, then in an in-depth fashion to categorize words, phrases, and sentences into codes based on the identified facilitators and barriers to mHealth adoption. A directed content analysis approach[112] to analyzing FG data will be used. Content analysis is a well-established method for analyzing qualitative data and is widely employed across the social, behavioral, and biomedical sciences.[113,114] Subsequently, it will be analyzed using NVivo to identify new themes related to (1) access to mobile technologies; (2) barriers and facilitators to adoption of mHealth tools; and (3) types of acceptable feedback during mHealth interventions. Information gleaned from the FGs will be used to design the nature – such as frequency, duration, scheduling time - and exact content of the feedback loops incorporated in the pilot feasibility study. All transcription data will be stored anonymously and backed up on the Yale server. All audio files will be destroyed using procedures set in place by Yale University after they have been transcribed and listened to.

Specific Aim 2: ***To conduct a 12-week pilot feasibility RCT among a sample of PLH with CUDs that will examine the impact of mHealth tools (cellular-enabled smart pill boxes and cell phones) and feedback (no feedback vs. automated feedback vs. automated + clinician feedback vs. automated feedback + text-reminder from a designated social network member) on primary (ART adherence and persistence) and secondary outcomes (HIV VS, cocaine use, retention in HIV care and in trial).***

All 90 participants for the pilot RCT study will be recruited from New Haven-area community HIV clinics, the Ryan White Consortium, and substance abuse treatment (SAT) centers. As indicated in the gender and minority inclusion statement, women and minorities will be represented in all sites of recruitment. The minimum age is 18 years of age, thus children 18-21 years old will be eligible for participation.

2.A. Recruitment Procedures: Similar to the recruitment procedure for the FGs IRB-approved flyers containing a toll-free number will be posted in numerous venues such as community SAT centers and HIV care clinics. Centers that have collaborated with us before and have been prime sites of recruitment include the Nathan Hale Clinic, Haelen Center, Hill Health Center, Central Medical Unit, Fair Haven Clinic, most of which are included in the Ryan White consortium. Due to our continued presence in New Haven through the implementation of several treatment programs and clinical trials, we are confident of being able to recruit participants for the pilot RCT. If enrollment is insufficient, we will post an announcement in "Did You Know?" – an electronic newsletter managed by Karina Danvers, Director of the New England AIDS Education and Training Center - Local Performance Site - that is disseminated regularly to New Haven-area clinics. This will help us reach all the local area HIV clinics that can refer potential participants to our study.

In addition to the above-mentioned recruitment sources, we will also be able to recruit from the Community Health Care Van (CHCV). The CHCV, a 36-foot van is equipped with two exam rooms, a counseling/phlebotomy room and a waiting area. The staff has developed strategic liaisons with patients and providers throughout the community and is capable of connecting researchers with potential HIV-infected patients with co-occurring substance abuse issues.

2.B. Screening Procedure: The initial screening eligibility criteria will include the following: (1) HIV+, (2) self-reported cocaine use in the past 6 months, and (4) speaks English or Spanish. If an individual meets the initial screening criteria, they will be invited to meet with a research assistant (RA) to determine if they fulfill all the necessary eligibility criteria to be included in the study.

Eligibility Criteria:

Inclusion Criteria	Exclusion Criteria

• Age ≥ 18 years • Clinic-confirmed HIV diagnosis • Currently prescribed or eligible for ART • Currently has insurance • Self-reported cocaine use ever • Willing and able to use a cell phone and blister pack for the 12-week intervention	• Unable to provide informed consent • Verbally or physically threatening to research staff • Unable to communicate in either English or Spanish

2.C. Informed Consent and Enrollment Procedures: All participants must be able to provide informed consent to be enrolled in the study. The RA will obtain informed consent and then explain the purposes, protocol, expectations, and possible risks and benefits of the study.

2.D. Randomization: Although a specific randomization process is not required for pilot RCTs, we want to ensure that crucial covariates that might influence our outcomes are controlled for a priori, especially given the modest sample size proposed in this pilot. Since it has been well-documented that individuals with underlying mental illness experience worse outcomes, we will minimally stratify based on the presence or absence of neurocognitive impairment. Randomization will be 1:1:1:1 to patients receiving either no feedback, automated feedback or automated + clinician feedback, and automated feedback + text-reminder from a social network.

2.E. Study Procedures:

1. *Baseline Interview:* After the informed consent procedure, participants will be asked to sign a medical release of information (ROI) to allow research staff to confirm self-reports of HIV status, medication prescription and healthcare utilization and to be able to communicate with the participants' clinical providers. The RA will then conduct the baseline interview consisting of various self-reported measures including demographic information, health care status, medical history, standardized measures for drug use and mental illness, and Information Motivation Behavioral (IMB) constructs for adherence. Participants will also undergo phlebotomy.

2. *Intervention:* After randomization, the RA will provide each subject with the following in order to commence the intervention part of the pilot feasibility study: a monthly prescription blister pack and a cell phone (specifically, an Android smartphone). Participants can choose to use their own phones if they already have an Android-based smartphone. The RA will teach the participants how to use blister pack and the smartphone (including using the voicemail and text messaging features).

- RAs will contact the medical providers for prescriptions, which will be sent to the local pharmacy (see section on Smart Pill Box Refills below). The local pharmacy will create medication blister packs. Participants will receive text feedback from the study + text-reminder from social network.

- We will use a text messaging system (Telerivet) to send text reminders to take pills at the dosage time. Information about dosage times will be collected by RA's during the baseline interview time.
-
- We will collect adherence data by counting pills in the blister-pack, a traditional and widely used method in the medication adherence literature. However, instead of manually counting the pills, the participants will take a picture of their blister-pack and text that picture to our study phone number. The participants will send this picture once a week for the intervention period (12 weeks) and the follow-up period (4 weeks). After downloading the pictures from the study phone, we will use image analysis techniques to count the pill(s) in each bin. We will send automated reminders for taking medication and texting the picture.

During the intervention period (12 weeks), a text messaging system (Telerivet) will text all participants once a week on their smartphones to take a brief survey using an app on their smartphones. CommCare is a cloud-based mobile messaging platform that allows a research team to set up an SMS gateway phone. This gateway phone allows the research team to conduct bulk messaging to participants via the telerivet app on one smart phone that has a sufficient data plan. The telerivet app on the gateway phone is directly linked to a Telerivet account that is accessed and managed via the web. The phone number of the participant is loaded into the Telerivet account at baseline, and the Telerivet system is then able to send them automatic reminders on their chosen day via the gateway phone.

This survey app will be designed on the open-source CommCare platform. The day and time of the weekly reminder will vary according to each subject's convenience and preference. The interview questions will utilize a multiple-choice format and participants will be able to use their smart phone screen to answer the questions. The questions will assess the following: (1) cocaine use in the past seven days, (2) triggers of cocaine use, (3) protected and unprotected sexual intercourse following cocaine use, (4) ART adherence in the past 7 days, and (5) reasons for non-adherence (options for non-adherence will be given with numbers associated with them for ease of answering (e.g. Press *"1 if you forgot", Press "2 if you ran out of medicine"*, etc.; as well as an *"other"* option). For participants in Groups A and B, the survey response will only be recorded; however, for participants in Group C, the survey app responses will be assessed each week by the RA who in turn will communicate the results to a clinical nurse. The clinical nurse will be funded through this study; he/she will be responsible for providing personalized feedback to all Group C participants. The clinic nurse will contact the subject with appropriate feedback about their health behavior and suggestions for sustained adherence. The specifics of this clinician feedback will be established from the FG findings (Aim 1). Thus, the purpose of the weekly survey app is two-fold – to assess self-reported ART adherence and to inform the clinician feedback. The participants in Group D will be in an intervention called, **'TRIDENT' (Text Reminder In DEsignated NeTwork)**. The following protocol is developed for this arm: i) Telerivet will send a weekly notification to the cell phone of their designated social network member as a prompt to send intervention text-reminder to the participant. ii) The social network designee will be asked to send the intervention text message within one

hour, for example, *'take your medications'*, to the participants. No fixed text or personalized text messages from the social network designee have not been developed for the intervention. Instead, the actual content of the text between the patient and the designee will be recorded as the intervention data.

After the 12-week intervention, all participants will be followed for a 4-week period and primary and secondary outcomes will also be recorded during the post-intervention follow-up period.

3. *Monthly Research Interviews:* Monthly interviews will take place for the 16-week duration of the study (12-week intervention and 4-week follow-up) for all participants. The interviews will include health care utilization, phlebotomy, self-reports of drug use, and mental illness. All phlebotomy information obtained after community release will be obtained through Quest Diagnostics, a national reference laboratory. We have a prearranged system for phlebotomy, reporting of results and storing specimens at -70C that has been in place for the past decade. None of the assays used are experimental and will be drawn as part of clinical care at standardized times as outlined. Tests will include HIV-1 RNA testing (Amplicor 1.5, range 50 to 750,000 copies/mL) and CD4 lymphocyte count using flow cytometry at baseline, end of intervention (12 weeks) and end of follow-up period (16 weeks). HIV genotypic mutations will be assessed at baseline and at 16 weeks (if VL>500 copies/mL).

4. Monthly Text-Message Data Collection: At weeks 4, 8, and 12, the following two types of research data will be collected from the participants. A total of 4 text messages (one text message per week) sent by the designated social network member to the participant will be downloaded. The text messages will be downloaded by a RA from the participant's cell phone. In order to pull participant text message/ SMS data off of the project phones, the research team will use a software called *SMS Backup and Restore*. With consent, this software will be installed only on the phones of participants in the fourth arm. The *SMS Backup and Restore* application allows us to connect the text message/SMS data on the participant phones to a secure Dropbox account. Our technical consultant will create these secure Dropbox accounts for every participant phone in the 4th arm and link them to each of the participant's phones. These Dropbox accounts will be protected with a unique password; the only individuals with access to the password and the accounts will be the project staff. During the monthly interviews with participants, the Research Assistants will navigate to the *SMS Backup and Restore* application on the participants' phones and backup the local SMS data to the Dropbox accounts. This is a two-step functionality within the *SMS Backup and Restore* application. The RAs will first click on "Backup" and then will be prompted to choose a location to sync the data to. The RAs will choose to backup the SMS data to the secure Dropbox that will already be linked to the phone. For more details, see the sections on "Risk, Minimizing Risk, and Data and Safety Monitoring Plan".

[redacted]

[redacted]

Individual activities	**Time (in weeks)**													
	Pre-intervention	Intervention												Follow-up
		0	1	2	3	4	5	6	7	8	9	10	11	12	16
Enrollment	X														
Chart review	X														X
Phlebotomy	X													X	X
Baseline interview	X														
Provide Blister pack		X												X	
Smartphone survey			X	X	X	X	X	X	X	X	X	X	X	X	X
SMS/Text download (only for fourth arm)						X				X				X	
Monthly interviews						X				X				X	X

[redacted]

[redacted]

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Aim 1 (Focus Groups): We will conduct six FGs, four with HIV+ cocaine users and two with healthcare providers, comprised of 6-8 persons each. For the PLH FGs, we will recruit PLH who primarily use cocaine, from clinical care and community outreach programs in New Haven, CT. Of the four PLH FGs, one will consist solely of men and one solely of women in order to address possible gender differences. Eligibility criteria will be: a) ≥18 years; (b) speaks English or Spanish; c) HIV+; d) self-reported cocaine use in the previous 30 days; and e) able to give informed consent. For the two healthcare provider FGs, we will recruit physicians, nurses, clinic supervisors, and substance abuse counselors from HIV clinics. We will target representation from the 5 HIV clinics in New Haven.

Aim 2 (Pilot Feasibility Study): We will recruit 90 participants from HIV care clinics and drug treatment programs in New Haven. Eligibility criteria will include: 1) clinic-confirmed HIV diagnosis; 2) ≥ 18 years; 3) prescribed or eligible (clinician willing to prescribe) for ART; 4) currently have inbsurance coverage; 5) self-reported cocaine use in the past 6 months; and 6) and willing and able to use an electronic pill box and blister pack for study duration. This will be a 16-week study with a 12-week intervention and 4-week post-intervention observation period.

Sample Size and Power Calculations: The literature suggests that effect size calculations may not be appropriate for pilot RCTs.[115] Thus, based on a review of pilot studies that have ranged in sample size from 12 per group[116-118] to 9%-50%[119,120] of the proposed larger RCT's sample size (generally 30 per arm); we propose to enroll 20 participants for groups A, B, and C. For Group D, we propose to enroll 30 participants so that hypotheses #7 (There is statistically significant difference between a patient's ART adherence and persistence and HIV outcomes when their designated social network member lives inside vs outside patient's activity space) can be tested. Therefore, a total of 90 study participants for the pilot feasibility RCT is proposed. This sample size is appropriate in order to refine study procedures, develop a final intervention manual and prepare for a future large-scale RCT.

[redacted]

[redacted]

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Aim 1 (Focus Groups): An initial set of 4 focus groups (FGs) comprised of 6-8 persons with HIV+ cocaine users and lasting one hour each will be conducted. Recruitment, screening, enrollment and other procedures for these FGs are discussed below. A second set of two FGs will be conducted among healthcare providers including physicians, nurses, clinic supervisors, and substance abuse counselors from HIV clinics.

Eligibility Criteria for Focus Groups of HIV-infected Cocaine Users:

- Age ≥18 years old
- HIV+
- Current cocaine use (in the past 30 days)
- Able to speak English or Spanish
- Able to provide informed consent

Eligibility Criteria for Focus Groups of Healthcare Providers:

- Currently employed as community-based HIV physician, clinician, healthcare worker, clinic supervisor or substance abuse counselor
- Speaks English or Spanish
- Able to give informed consent

Aim 2 (Pilot Feasibility Study): The initial screening eligibility criteria will include the following: (1) HIV+, (2) self-reported cocaine use in the past 6 months, and (4) speaks English or Spanish. If an individual meets the initial screening criteria, they will be invited to meet with a research assistant (RA) to determine if they fulfill all the necessary eligibility criteria to be included in the study.

Eligibility Criteria:

Inclusion Criteria	Exclusion Criteria

• Age ≥ 18 years • Clinic-confirmed HIV diagnosis • Currently prescribed or eligible for ART • Currently has insurance • Self-reported cocaine use ever in lifetime • Willing and able to use a cell phone and blister pack for the 12-week intervention	• Unable to provide informed consent • Verbally or physically threatening to research staff • Unable to communicate in either English or Spanish

8. How will **eligibility** be determined, and by whom?

Aim 1 (Focus Groups): Individuals interested in participating in the FGs will be able to call the toll-free number listed in the flyers, during which they will be asked a number of screening questions by the study RA, including a) age, b) gender, c) HIV status, and d) cocaine use in the past 30 days. If initially eligible, they will be provided with more study details and invited to participate in the FGs. No specific screening will occur for the community-based clinicians and healthcare providers other than a request to provide proof of identity to verify their designations. Prior to the FG, informed consent will be obtained verbally by the RA who will explain the purpose, protocol, expectations and possible risks and benefits of the study. Verbal consent will be used to avoid the use of real names in the FGs and ensure confidentiality. Participants will be provided an informed consent form that will be approved through local authorities and the Yale University School of Medicine Institutional Review Boards (IRB). The consent form will outline the agreement to participate in this study. All patients will be reminded that their refusal to participate in no way will negatively affect their relationship with any of the participating agencies or clinics, substance abuse treatment or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future.

Aim 2 (Pilot Feasibility Study): Individuals interested in participating in the pilot study will be able to call the toll-free number listed in the flyers, during which they will be asked a number of screening questions. Eligible participants will be asked if they would like to participate and will be referred to a study RA to definitively assess them for eligibility. Referral will be conducted by asking the subject to sign a release of medical and drug treatment information form. After explaining the details of the study, informed consent will be obtained either by the RA or the PI. These persons will explain the purposes, protocol, expectations, and possible risks and benefits of the study. Participants will be provided an informed consent form that will be approved through the Yale University School of Medicine Institutional Review Board (IRB). The informed consent form will outline the agreement to participate in this research study. All patients will be reminded that their refusal to participate in no way will negatively affect their relationship with Yale University and local alcohol drug treatment or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Risks Associated with Focus Groups: During the FG sessions with PLH who use cocaine, topics such as cocaine use and substance use treatment will be discussed. These topics may make participants feel uncomfortable. Participants may choose not to answer all or any part of a question during the sessions. There are minimal risks expected from participating in the study such as feeling uncomfortable in certain topics being discussed. If anyone feels uncomfortable, they may choose not to answer any part or all of a question. Participant names will not be used or recorded in the focus groups. Instead, FG participants will be asked to use a pseudonym/nickname. Yale IRB-approved fliers will be used to help with recruitment for focus groups and the drug treatment counselors will also assist in recruitment of participants. When recruiting participants from venues, the participants will be briefly told about the FG and if they want to learn more about it, recruiters will hand out a contact information card to call into the study site. No information will be collected from them at this time so they may choose to not to call into the site or if they do call in and want to come in for consenting, information is still not collected and they may decline to come in. During the consent process, they will be read the consent form verbatim and will be asked if they would like to participate in the study or not. They will also be able to decline or take more time to think about it. If they verbally consent, another appointment will be scheduled for the participant to come in and participate in the focus group. They may choose to withdraw from the study at any point and decide not to come in for the focus group session. During the FGs, participants may choose not to answer a question or part of a question and are free to give as little or as much information as they feel comfortable doing. No study-related unanticipated problems or adverse events are expected to occur in this part of the study. Real names will not be used during the FGs and answers to questions will not be linked to a participant's real name. Transcripts will be linked only to pseudonyms or nicknames. Hard copies of data collected will be stored in a locked cabinet. Electronic copies can be accessed by providing a user identification and password. For FGs involving community healthcare providers and clinicians, similar attention to confidentiality will be given.

Risks Associated with Pilot Feasibility Study

1. Risks Associated with Standardized Assessments: The standardized assessments administered during baseline and monthly research interviews will include: (1) demographic information, including age, race, and gender; (2) health care status, including past medical history, current medications, (3) standardized screening for mental illness using the Center for Epidemiologic Studies Depression Scale (CES-D);[121] (4) standardized measures of drug use, including determination of DSM-V criteria for cocaine use disorder;[122] (5) Addiction Severity Index (ASI)-Lite to assess cocaine use, polysubstance use and severity;[123,124] (6) LifeWindows questionnaire to measure the Information-Motivation-Behavioral constructs of adherence;[111,125] (7) ART adherence using blister pack , Visual Analog Scale (VAS) and brief adherence scale;[126,127] (8) change in cocaine use using the Timeline Follow-Back (TLFB);[128] (9) AUDIT-C to assess alcohol use;[129] (10) health literacy;[130] (11) social support;[131] (12) trust in physicians;[132] (13) acceptance of smart pill box and smartphones;[133] and (14) perceived source credibility[134], (15) neighborhood delineation using the Activity Space; and (16) mapping and interpreting social or personal networks using a egocentric social network analysis questionnaire. It is possible that participants may feel uncomfortable answering these questions; in this case, they will be able to refuse answering any questions that they do not wish to answer.

2. Risks Associated with Interviews: During the baseline and monthly research interviews, topics such as cocaine use and substance use treatment will be discussed. These topics may make participants feel uncomfortable. Participants may choose not to answer all or any part of a question during the interviews. There are minimal risks expected from participating in the study such as feeling uncomfortable in certain topics being discussed. If anyone feels uncomfortable, they may choose not to answer any part or all of a question. Participant and designated social network member's names will not be used or recorded in the interview data; instead participant study numbers will be used. Yale IRB-approved flyers will be used to help with recruitment for the RCT and the drug treatment counselors will also assist in recruitment of participants. When recruiting participants from venues, participants will be briefly told about the study and if they want to learn more about it, recruiters will hand out a contact information card to call into the study site. No information will be collected from them at this time so they may choose to not to call into the site or if they do call in and want to come in for consenting, information is still not collected and they may decline to come in. Prior to obtaining informed consent, the participant will be read the consent form verbatim and will be asked if they would like to participate in the study or not. They will also be able to decline or take more time to think about it. If they agree, they will be asked to sign the consent form. They may choose to withdraw from the study at any point.

3. Risks Associated with Loss of Confidentiality: As with all research, there is a risk that involves potential breaches of confidentiality. We intend to do everything possible to reduce this risk and this is one of the process measures we propose to measure. All study assessments will be administered in a private setting that will minimizes breaches in confidentiality. Patients with substance use disorders, including cocaine, are a vulnerable population. Thus, our research to date has insured strict confidentiality safeguards. We will further increase the protection of these participants by obtaining a Certificate of Confidentiality.

Participants' confidentiality will be well protected at our research offices in New Haven. Studies that are currently underway at these sites include trials for the treatment of opioid, alcohol and CUDs. Additionally, there are studies that involve both HIV+ and HIV- patients, those that have been involved and uninvolved with the criminal justice system as well as those with and without mental illness. Thus, the entry into our research offices will not identify our participants as belonging to one or another class of citizens. While within our research offices, we implement a number of additional safeguards. First, participants will be interviewed in a private room in a research setting where participants for a number of research projects are conducted with HIV+ and HIV-, HCV+ and HCV- and drug using and non-drug using participants. Potential sites for breaches of confidentiality include during the study interviews at our research storefront. Our New Haven study site is handicap accessible and has two possible entrances that may be used for entry and exit from the building. The research environment ensures that confidentiality is protected in that each person enters individually through the front door, goes immediately to the computer workstation, and then to the interview room. Appointments are staggered to avoid participant encounters in the hallway. Participants have the option of leaving through a different doorway from the one they entered. All information is stored in password-protected, PGP encrypted computers with double-password protection for opening specified files. All confidential information (study instruments, pharmacy records, etc.) will be recorded with study participant number only and maintained in locked cabinets within our offices at the Yale University AIDS

Program and will only be available to be opened by the Data Manager, Project Director or the Principal Investigator. Electronic databases will be maintained through password-protected computers and files and maintained at the Yale University AIDS Program.

To help us protect participant privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health on May 22, 2017. The researchers can use this Certificate to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify participants, except as explained below.

The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of *events associated with child abuse and neglect, or harm to self or others*.

4. Risks Associated with Phlebotomy: As part of routine care, patients will undergo phlebotomy. Patients may experience discomfort or bleeding at the site. Since no additional laboratory results are being obtained other than those that would be used for routine clinical care, this poses no additional risk to the subject.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Aim 1 (Focus Groups): There are minimal risks expected from participating in the FGs such as feeling uncomfortable with certain topics being discussed. As mentioned previously, all participants recruited for FGs will be reminded that their refusal to participate in no way will negatively affect their relationship with any of the participating agencies or clinics, substance abuse treatment or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future. If participants do feel uncomfortable about certain questions asked during the FGs, they will be able to choose not to answer the question that makes them uncomfortable. FGs will be conducted in private rooms to ensure the confidentiality of the participants. All focus group and survey data will be stored in secure locations. To address the possibility of individuals coercing others to participate, all participants will be asked to confirm that they are coming forward out of their own free will and will be given the option not to continue with the study at any point. Individuals, who may go on to recruit others, will also be instructed not to coerce members of their network into coming forward to participate in the study. Of note, no one in the FGs will be asked for their name or any specific Identifier since this is a one-time assessment and we do not need to contact the subject for follow-up interviews. At the FGs, they can either provide their real name or make up a name. During the FGs, rules will be established at the outset and all participants will be told that the meeting is confidential and that any personal information shared would not be shared with others. We will explain that confidentiality is key, so as to allow everyone to feel comfortable in sharing their opinions.

Aim 2 (Pilot Feasibility Study): Standardized interviews will take place in a confidential setting in our research office in New Haven. Our research staff has completed IRB and HIPAA training

and we have put in place rigorous procedures for protecting data at the Yale University AIDS Program that have resulted from years of conducting research with vulnerable populations. All confidential information (study instruments, pharmacy records, etc.) will be recorded with study participant numbers only and maintained in locked cabinets within our offices at the Yale University AIDS Program and will only be available to be opened by the Data Manager, Project Director or the Principal Investigator. All clinical information will be stored in locked file cabinets. Electronic databases will be maintained through password-protected computers and files and maintained at the Yale University AIDS Program. The adherence data obtained through text messaging will be saved in the research team's server associated with Yale University. Similarly, the smartphone survey data will be saved on a central secure server owned by Dimagi, Inc. and will be accessible only to the study researchers. Additionally, for text message/SMS data download: a two-step process (secure Dropbox and unique password to access available only to the research team) leveraging the *SMS Backup and Restore* application will ensure that the participant SMS data is never downloaded locally to a non-University machine and will also ensure that it is never stored on a non-vetted third party server.

The project staff will remove all SMS messages from this file that are sent from phone numbers that do not match with someone (social network designee) who has consented to have their information shared with the research team. In addition, all the text messages will be "shredded" using PGP Desktop Shred which removes all traces of the file on the computer.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

    The anticipated risks associated with this study are deemed overall to be low. Since the intervention does not utilize any pharmacology therapy, there is no scope for unintended medication side-effects. The assessment of risk does not, however, preclude the potential for anticipated and/or unanticipated adverse events, serious or otherwise, since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. The proposed RCT is a single-site investigation. As such, it does not require an independent Data and Safety Monitoring Board (DSMB), however it is essential to have a Data and Safety Monitoring Plan (DSMP).

    Some of the factors we intend to monitor closely include: 1) Are the treatment groups comparable at baseline; 2) Are the accrual rates meeting initial projections and is the trial on its scheduled timeline; 3) Are the data of sufficient quality; 4) Are the treatment groups different with respect to efficacy data; 5) Is there an indication to discontinue the trial due to predefined criteria; and 6) Should the protocol be modified in response to any unanticipated outcome or change in temporal event?

    Listed below are a number of items that potentially could be an adverse event for participation in this study:

    a. Subjects whose cocaine use imposes risk to themselves: We will continue to enroll the subject in their randomized arm of the study according to protocol; however, we will refer

them to more intensive counseling. For participants who become unstable with their cocaine use, they will be offered transfer to an inpatient drug treatment program where more structure can be provided to meet their drug treatment goals.

b. Plan for subjects who develop serious psychiatric/medical symptoms during the follow-up phase: If the subjects develop serious DSM-V psychiatric symptoms or medical symptoms they will have many opportunities to report their symptoms with not only the clinicians but also the RA who will be available 7 days a week by telephone. If serious symptoms are reported, the participants will be evaluated by the PI of the study, Dr. Altice who is board-certified in Internal Medicine, Infectious Diseases and Internal Medicine. If Dr. Altice determines that the subjects' medical or psychiatric symptoms cannot be treated as outpatients, they will be admitted to the local hospital Emergency Room. Furthermore, the subjects' chronic medical primary care providers will be notified immediately of any changes in their psychiatric or medical condition to continue with follow-up.
c. Notification to HIV physicians due to lack of ART adherence or persistence: During the RCT, if participants are found to be non-adherent or non-persistent to their ART medication, where a risk of HIV virus can mutate to become resistant to the current regiment, their physician will be notified.[135] When an individual is enrolled in the study, he/she will be asked to provide us with the name of their physician and sign a medical release of information (ROI) allowing us permission to communicate with the physician as need. A letter will be faxed to the physician's office stating that the participant is enrolled in an ART adherence study; this initial communication will also request notification of any medication changes. Additional communication with the provider will include phlebotomy results and information if the participant is found to be non-compliant to their ART regimen (missed 2 weeks or more of medications).
d. Halting Rules for the Study: A DSMP, similar to a DSMB, may institute a number of pre-planned rules for halting the study or modifying the study design. For pilot studies of this size, when there is not expected to be a difference in efficacy anticipated, there will be no halting rules aside from adverse events. For the purposes of this study, a pre-planned interim analysis is planned when 50% of the subjects are accrued and have completed 6 weeks of the study. This time point is based upon efficacy outcomes when the primary measure of interest can be assessed.
e. Confidentiality of research data: Breaches of confidentiality regarding research data are more difficult to detect. For that reason, we have in place a number of safeguards including double-locked doors, locked file cabinets, confidential and dedicated fax machine and double password-protected computers. In accordance with federal and university policy, all research personnel are compliant with HIPAA training. If any breach of data confidentiality were detected, we would use similarly detailed procedures for report to the PI and IRB simultaneously.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Aim 1 (Focus Groups): The audio files from all of the FGs will be sent to a licensed HIPAA-compliant professional transcription service using secure and encrypted transfer systems. After transcription, audio recordings of the FG discussions will be first locked in double protected cabinets and destroyed after verification of the information. After transcription of all FGs, content

analysis – a technique designed to uncover meaningful patterns and themes. Transcribed text will be coded into themes using an iterative process. The text will first be reviewed in a preliminary review, then in an in-depth fashion to categorize words, phrases, and sentences into codes based on the identified facilitators and barriers to mHealth adoption. A directed content analysis approach[112] to analyzing FG data will be used to identify patterns and themes in the data based on the categories of interest, to extend the IMB model to the mHealth context. Content analysis is a well-established method for analyzing qualitative data and is widely employed across the social, behavioral, and biomedical sciences.[113,114] Subsequently, it will be analyzed using NVivo to identify new themes related to (1) access to mobile technologies; (2) barriers and facilitators to adoption of mHealth tools; and (3) types of acceptable feedback during mHealth interventions. Information gleaned from the FGs will be used to design the nature – such as frequency, duration, scheduling time - and exact content of the feedback loops incorporated in the pilot feasibility study. All transcription data will be stored anonymously and backed up on the Yale server. All audio files will be destroyed using procedures set in place by Yale University after they have been transcribed and listened to.

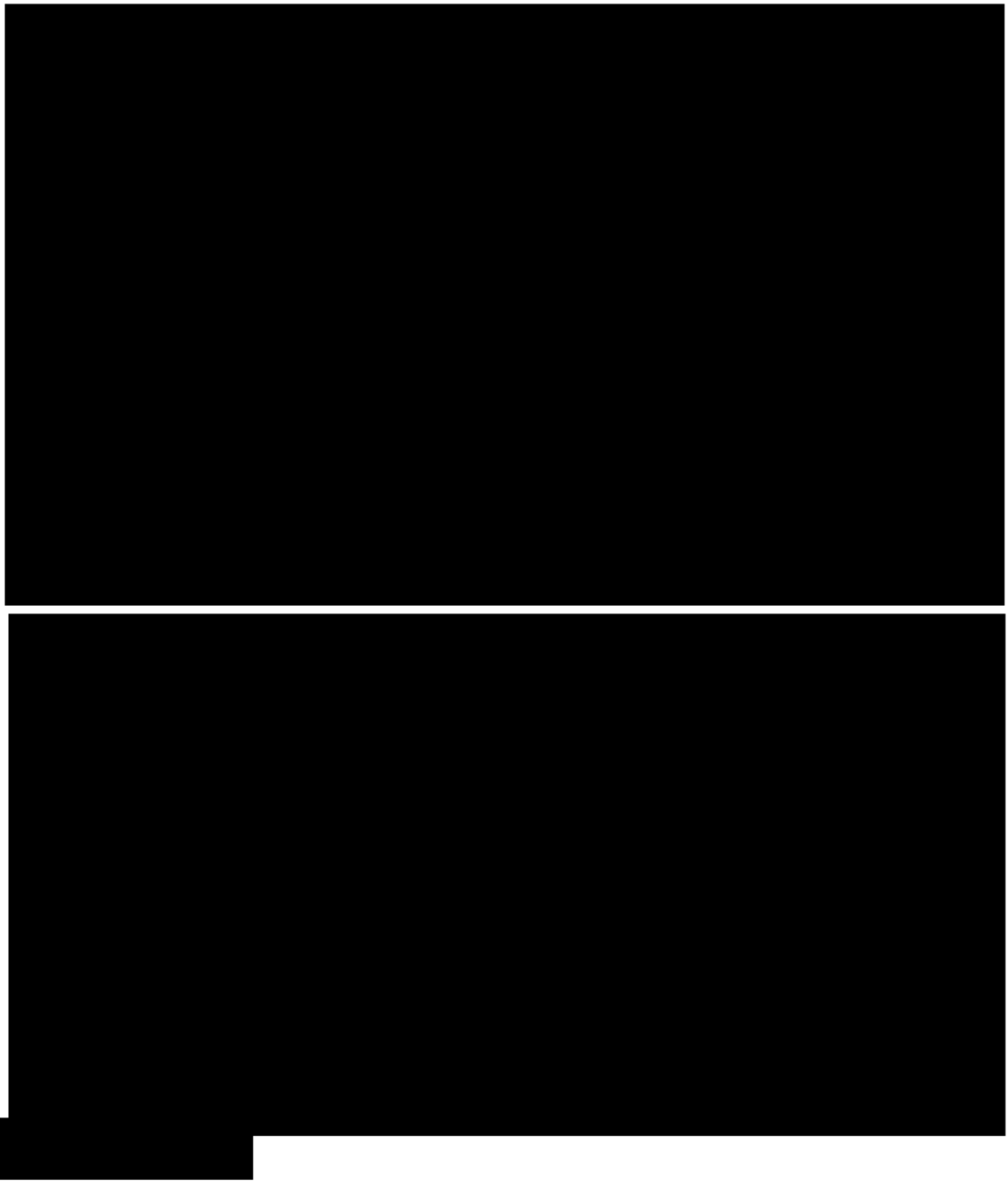
Aim 2 (Pilot Feasibility Study): The primary outcomes will be ART adherence and persistence, measured as a composite score ranging from 0 to 100%, and as number of continuous days taking ART without a 7-day (or 3-day) gap[18,71] respectively. Outcome analyses will be conducted for (a) adherence and persistence behavior, (b) drug outcomes (cocaine use), (c) HIV treatment outcomes (VL<20 copies/mL; change in CD4+ T lymphocytes), and (d) ART-related Information, Motivation, and Behavioral Skills constructs. The general framework for discerning differences between study conditions on main outcome variables will be to perform 3 (intervention condition) x 3 (repeated follow-up assessments) mixed design analysis entering pre-intervention scores as covariates and additional theoretically and empirically relevant covariates (such as baseline mental status etc.). For variables that are approximately normally distributed, we will use multivariate analyses of covariance (MANCOVA), with significant multivariate tests followed by subsequent analyses of co-variance (ANCOVA). Variables that violate distributional assumptions of normality will be analyzed using generalized linear model (GLM) procedures, which enable the use of non-Gaussian error models. Based on a review of the literature, GLM is the most appropriate approach for variables with strong positive skew, e.g., adherence.

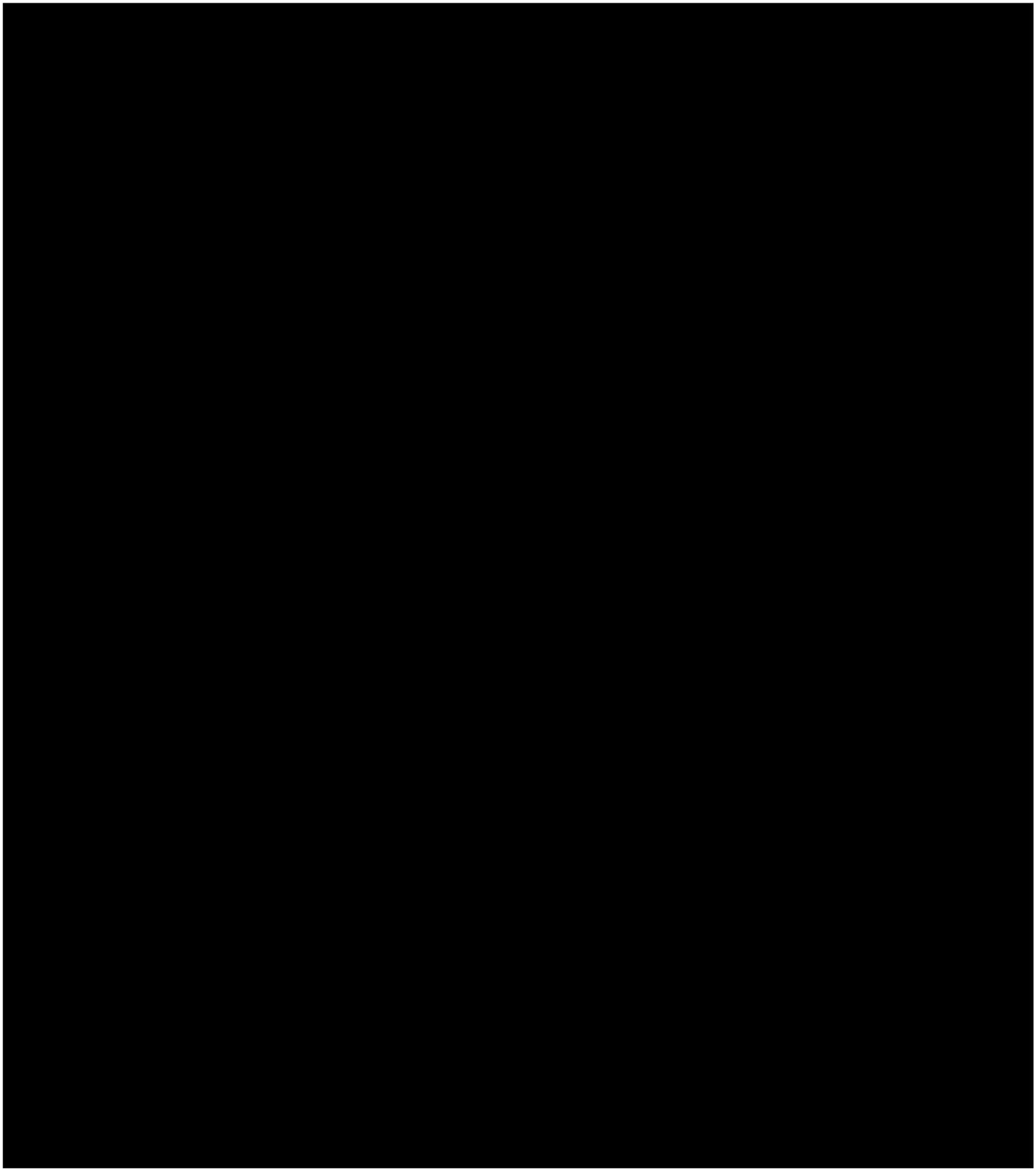
To examine the mediating and moderating effects of activity space and social network facilitators and barriers on primary (ART adherence and persistence) and secondary outcomes (HIV viral suppression, cocaine use, retention in HIV care), the following steps are going to be followed:

a. A range of variables associated to activity space and social networks (both risk and support) will be calculated using a combination of GIS, SNA, and spatial statistics methods. The variables will be the covariates.
b. The outcome variables are: primary (ART adherence and persistence) and secondary outcomes (HIV viral suppression, cocaine use, retention in HIV care).
c. We will first use descriptive statistics, bivariate correlation, and t-tests to understand the distribution and association of all the covariates calculated in step#a with the outcome variables (step#b).
d. After running tests of multicolinearity, only uncorrelated covariates at $p \leq 0.05$ (considered statistically significant) will be included in the subsequent mediation and moderation analysis.

e. Using the framework of structural equation modeling, we will identify the moderating and/or mediating effects of spatial (activity space and neighborhood levels) and non-spatial data (individual and interpersonal) covariates on the primary and secondary outcomes.

A comparative analysis will be conducted to contrast the model performance (R2, AIC, and RMSE) of two mediation/moderation models with the primary (ART adherence) and a secondary (HIV viral suppression) outcome:1) with social network metrics and b) with spatial-social network metrics (calculated in step#a).





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SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol___
   Aim 1 (Focus Groups): 42 (30 PLH cocaine users; 12 healthcare providers)
   Aim 2 (Pilot Feasibility Study): 90 PLH with co-occurring CUD

   b. If this is a multi-site study, give the total number of subjects targeted across all sites___

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers
☐ Posters
☐ Letter
☐ Medical Record Review
☐ Departmental/Center Newsletters
☐ YCCI Recruitment database
☐ Other (describe):

☐ Internet/Web Postings
☐ Mass E-mail Solicitation
☐ Departmental/Center Website
☐ Departmental/Center Research Boards
☐ Web-Based Clinical Trial Registries
☐ Clinicaltrials.gov Registry (do not send materials to HIC)

☐ Radio
☐ Telephone
☐ Television
☐ Newspaper

Upon funding of this study, flyers will be created.

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.
b. Describe how potential subjects are contacted.
c. Who is recruiting potential subjects?

Aim 1 (Focus Groups): In order to recruit people the FGs of HIV+ cocaine users, IRB-approved flyers containing a toll-free number will be posted in a number of clinical and community venues including HIV and drug treatment clinics, our mobile medical unit, and community support groups. Due to our continued presence in New Haven through the implementation of several treatment programs and clinical trials, we are confident of being able to recruit participants for the FGs. For the FGs with healthcare providers, IRB-approved flyers containing a toll-free number will be posted in the offices of all five HIV clinics in the Ryan White Consortium. Providers from all sites have been successfully recruited and participated in previous FGs. We will also recruit through announcements in the electronic newsletter "Did You Know?" – an electronic newsletter managed by Karina Danvers, Director of the New England AIDS Education and Training Center - Local Performance Site - that is disseminated regularly to New Haven-area clinics.

Aim 2 (Pilot Feasibility Study): Similar to the recruitment procedure for the FGs, IRB-approved flyers containing a toll-free number will be posted in numerous venues such as community SAT centers and HIV care clinics. Centers that have collaborated with us before and have been prime sites of recruitment include the Nathan Hale Clinic, Haelen Center, Hill Health Center, Central Medical Unit, Fair Haven Clinic, most of which are included in the Ryan White consortium. Due to our continued presence in New Haven through the implementation of several treatment programs and clinical trials, we are confident of being able to recruit participants for the pilot RCT. If enrollment is insufficient, we will post an announcement in "Did You Know?" – an electronic newsletter managed by Karina Danvers, Director of the New England AIDS Education and Training Center - Local Performance Site - that is disseminated regularly to New Haven-area clinics. This will help us reach all the local area HIV clinics that can refer potential participants to our study.

In addition to the above-mentioned recruitment sources, we will also be able to recruit from the Community Health Care Van (CHCV). The CHCV, a 36-foot van is equipped with two exam rooms, a counseling/phlebotomy room and a waiting area. Partial support from NIDA (R01-DA10186) has enabled the CHCV project to expand service delivery and to reach a number of goals which improve the health care of out-of-treatment drug users. The program currently operates five days (and some evenings) a week in five underserved neighborhoods in New Haven. The CHCV is staffed by a full-time clinical coordinator, a drug treatment coordinator, a case

manager, HIV counselors, social workers, mental health workers, clinicians from several hospitals and community health care centers and a dedicated driver/outreach worker. The staff has developed strategic liaisons with patients and providers throughout the community and is capable of connecting researchers with potential HIV-infected patients with co-occurring substance abuse issues.

For the fourth arm, we will be asking the participants to provide us with three names of people in their social network, who has a phone and are willing to send them weekly text reminder to take their medication. Out of the three people, one person will be chosen by the RA to be the social designee. The RA will be contacting all three social designees via phone and upon verbal consent, the social designee will be provided information about the study and their role, and reminded to send text messages to the participants on the weekly basis.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

[redacted]

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Aim 1 (Focus Groups): Yale IRB-approved fliers will be used to help with recruitment for FGs with cocaine-using individuals and the drug treatment counselors will also assist in recruitment of participants. For the FGs with healthcare providers, IRB-approved flyers containing a toll-free number will be posted in the offices of all five HIV clinics in the Ryan White Consortium. When recruiting participants from venues, the participants will be briefly told about the FG and if they want to learn more about it, recruiters will hand out a contact information card to call into the study site. No information will be collected from them at this time so they may choose to not to call into the site or if they do call in and want to come in for consenting, information is still not collected and they may decline to come in. During the consent process, they will be read the consent form verbatim and will be asked if they would like to participate in the study or not. They will also be able to decline or take more time to think about it. If they verbally consent, another appointment will be scheduled for the participant to come in and participate in the focus group.

Aim 2 (Pilot Feasibility Study): Yale IRB-approved fliers will be used to help with recruitment for the RCT and the drug treatment counselors will also assist in recruitment of participants. When recruiting participants from venues, participants will be briefly told about the study and if they want to learn more about it, recruiters will hand out a contact information card to call into the study site. No information will be collected from them at this time so they may choose to not to call into the site or if they do call in and want to come in for consenting, information is still not collected and they may decline to come in. Participants will be provided an informed consent form that will be approved through the Yale University School of Medicine Institutional Review Board (IRB). The participant will be read the consent form verbatim and will be asked if they would like to participate in the study or not. The consent form will outline the agreement to participate in this research study. Participants will indicate consent by signing and dating the informed consent form. All patients will be reminded that their refusal to participate will not negatively affect their relationship with Yale University, local SAT or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future. They will also be able to decline or take more time to think about it. If they agree, they will be asked to sign the consent form. They may choose to withdraw from the study at any point.

In addition, the following process of consent is going to be followed for the designated social network member for the fourth arm intervention (TRIDENT): a) after randomized to the 4th arm, the RAs and/or the Project Coordinator will ask the participant to call his/her designated social network member, b) the participant will explain the study details from an information sheet to the designee. At this stage the RAs and/or the Project Coordinator will also help in explaining the role

of the designee in the intervention, c) We will obtain a verbal consent from the designees as minimal risk is involved. The risk is minimal for designees because: a) the designees are not answering any questions, b) they are not completing any surveys at the study sites, c) they will use their own phone to send text messages to the participant, d) the data from the messages will be downloaded from the patient's phone and not from the designee's phone, and e) after obtaining the verbal consent, the designee will be given an unique ID and their name or phone number will not be used.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

    The study interviewers are trained in interviewing and will assess the subject's understanding through verbal responses and non-verbal cues. Interviewers will ask open ended questions while introducing the details of the study to the subject such as "Can you tell me what you understood from our discussion?" or "What should you do if you want to stop participating in this study?" and will use IRB approved consent forms during informed consent procedure. If the interviewer determines that the subject does not fully comprehend the study purpose and his or her role as a participant, the subject will not be consented and will not be eligible for the study.

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    Aim 1 (Focus Groups): No signed consent forms will be required for the focus group participants since signatures would be the only identifiers. An IRB-approved consent form will be read verbatim and assent will be given verbally. Additionally, a copy of the consent form will be given to the participants.

    Aim 2 (Pilot Feasibility Study): A compound consent and authorization form will be used (attached in this application).

    No signed consent forms will be required for the designated social network members, involved in the 4th arm of Aim 2, since their health and personal identifiers are not used in the study. An IRB-approved information sheet will be read verbatim and assent will be given verbally. A unique ID will be provided for the designee and their names will not be used.

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

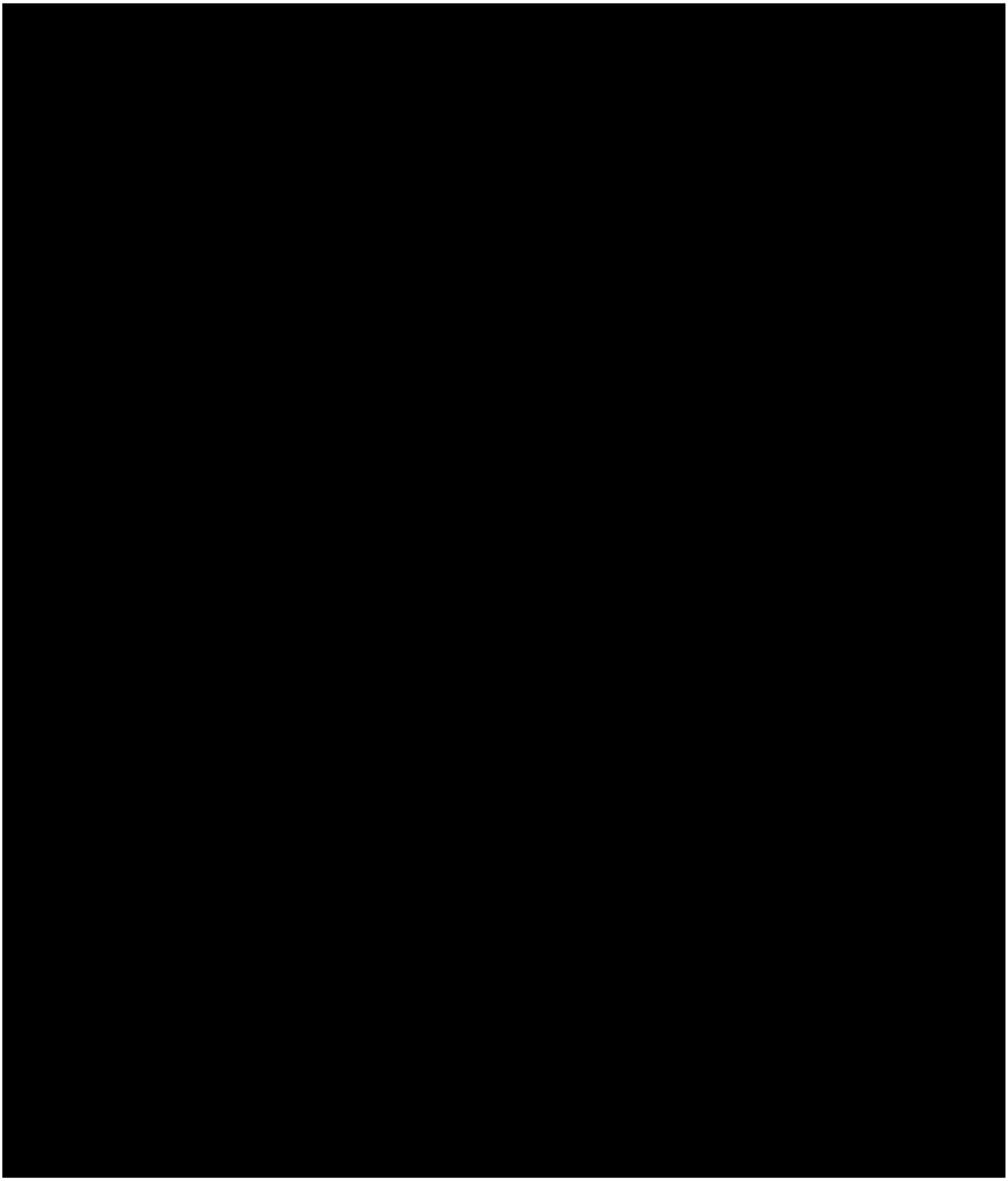
    All consent forms, information sheets and study documents will be available in English and Spanish. Our team consists of individuals who are bi-lingual/bi-cultural in Spanish and English.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.



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SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Private identifiable data about study participants including their names, age, sex, ethnicity, addresses, phone numbers and other contact information, photos, dates of birth will be collected. Names and phone numbers will be collected from social designee for the fourth arm. All confidential information (study instruments etc.) will be recorded with study participant number only, maintained in locked cabinets within our offices at the Yale University AIDS Program and will only be available to be opened by the Data Manager, Project Manager or the Principal Investigator.

b. How will the research data be collected, recorded and stored?

Aim 1 (Focus Groups): FG guides will be prepared that detail the conduct during and after the interview, including not using names, not discussing specific illegal activities, and maintaining the confidentiality of focus group participants. Materials will consist of interviews with the participants that have been described previously that will be audio-recorded and then transcribed. The audio files from all of the FGs will be sent to a licensed professional transcription service using secure and encrypted transfer systems.

Aim 2 (Pilot Feasibility Study): The research materials of interest in this study include structured questionnaire data (primarily using standardized and validated measures), laboratory data obtained at Quest Diagnostics laboratories, chart review, and biological measures obtained at research sites including urinary toxicology screens, data obtained through participants sending pictures of blister packs, and survey data obtained through the smartphone app-based survey. All such materials and questionnaire data (excluding laboratory data) will be specifically obtained for research purposes.

Data Sources:

1. *Structured Interviews*: Structured interviews will include: (1) demographics; (2) health status, including past medical history and current medications; (3) depressive symptoms using the CES-D;[136] (4) standardized measures of drug use, including determination of DSM-V criteria[122] for severity of cocaine use; (5) Addiction Severity Index (ASI)-Lite to assess cocaine use, polysubstance use and severity on HIV outcomes;[137] (6) ART adherence using the Smart Pill Box , Visual Analog Scale (VAS) and brief adherence scale;[126,127] (8) change in cocaine use using the Timeline Follow-Back (TLFB);[128] (9) AUDIT-C to assess alcohol use;[129] (10) health literacy;[130] (11) social support;[131] (12) trust in physicians;[132] (13) acceptance of smartphones;[133] and (14) perceived source credibility[134], , (15) neighborhood effects using the Activity Space questionnaire, and (16) egocentric social network inventory to understand support and risk networks.

2. Photos of blister pack: We will be asking participants to text the image of the medication blister pack every week. This method will be used to count the pills they have taken in the week, and hence, adherence will be determined using this source.

3. *Smart phone app survey*: During the intervention period, a smartphone app built on the open-source CommCare platform (powered by Dimagi, Inc.) will be used to collect weekly data from participants. The weekly survey data will be stored on HIPAA-compliant CommCare servers and transferred to Yale-secured and encrypted computers periodically. As per Yale HIPAA Privacy rules, Business Associates Agreements (BAA) will be established between vendors such as Dimagi, Inc., which will store the Protected Health Information (PHI) of the participants.

4. *Laboratory Measurements*: We have a prearranged system for phlebotomy, reporting of results and storing of specimens at -70C through Quest Diagnostics. Because tests are not experiment, all results (HIV VL, CD4 and genotypic analyses) will be sent to the participants' providers, including HIV-1 RNA testing (Amplicor 1.5, range 20 to 750,000 copies/mL) and CD4 lymphocyte count at baseline, and end of intervention (12 weeks) . HIV genotypic mutations will be assessed at baseline and at 16 weeks (if VL>500 copies/mL).
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5. *Chart Review*: During consenting procedures, a medical release of information (ROI) will be obtained to allow research staff to review medical records at drug and alcohol treatment, local hospitals, pharmacies and HIV care sites. Medical records will be retrieved to confirm self-reports of healthcare utilization, HIV status, documented medical history and prescribed medications. The ROI will allow us to communicate with medical, psychiatric and drug treatment providers to inform them that their patient will be in an adherence study, to alert research staff of any changes in ART medication, and in case of the participant becoming acutely ill.

6.Text messages/SMS download: A total of 4 text messages (one text message per week) sent by the designated social network member to the participant will be downloaded. The text messages will be downloaded by a RA from the participant's cell phone after receiving consent from the participants All phones are will be password protected and encrypted.

Storage of Data: All information will be stored in password-protected computers with double-password protection for opening specified files. The computers in our research facility have been encrypted in accordance to HIPAA guidelines. NetIDs of all research personnel will be provided to the IRB and to the IT Services for verification for encryption. If new members are added to the research team, and if personal computers were to be used for accessing PHI, all such machines will need to be Yale encrypted and verified by the IT service office. For the duration of the pilot study, medication adherence data obtained through the use of smart pill boxes will be stored in a secure, encrypted cloud system owned by TowerView Health® Corp. This data will be erased once it has been transferred securely to our research computers. Similarly, CommCare survey data will be saved on a central server owned by Dimagi, Inc. until it has been securely transferred to our computers. In addition, data collected from the Activity Space, and Social Network Questionnaire will be saved on Microsoft's cloud computing platform called University of Connecticut's (UConn) instance of Microsoft Azure, which is also compliant with UConn's and similar to Yale's HIPAA policy. UConn's UITS offers the use of a HIPAA approved

instance of Microsoft Azure as a service. A BAA from UConn will be provided to Yale IRB. We are using UConn's Azure service for the following reasons:

- Dr. Ghosh, a Co-PI/collaborator of this study, and her team from UConn have built an android based survey app using PowerApps, which is connected to UConn's Azure platform.
- The data that will be collected using this survey will be stored on UConn's Azure SQL database
- Only Dr. Ghosh has access to that database and uses her UConn's administrator netID to login.

. Text download/ SMS from participants (fourth arm) will initially be stored in a secure Yale Dropbox which will protected by unique password available only to the project staff.All research data will be stored in the double-locked research offices within the Clinical and Community Research Program within the Yale University AIDS Program. Client level data will be stored with the research study number and without any unique identifiers. All identifiers that link study number to study subject will be housed in PGP encrypted, password-protected computers available only to the Data Manager/Statistician, Project Director and the Principal Investigator. All computers used for study purposes have been PGP encrypted to meet all HIPAA requirements. During the 20 years of Dr. Altice's research experience, there has never been a breach in confidential data. The data will be stored in the manner noted above for at least seven years after completion of the study. All confidential information (study instruments, pharmacy record, etc.) will be recorded with the study participant number only and maintained in locked cabinets within our offices at the Yale University AIDS Program and will only be available to be opened by the Data Manager, Project Director or the Principal Investigator. These data will be analyzed so that the findings can contribute to scientific literature that could be used to develop effective interventions for HIV+ cocaine users. All files will be stored in locked cabinets in a locked facility.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

All information will be stored in password-protected computers with double-password protection for opening specified files. The computers in our research facility have been encrypted in accordance to HIPAA guidelines. For new personnel added to the team or use of personal computers will be encrypted by the ITS. For the duration of the pilot study, medication adherence data obtained through the use of smart pill boxes will be stored in a secure, encrypted cloud system owned by TowerView Health® Corp. This data will be erased once it has been transferred securely to our research computers. Similarly, the smart phone app survey data will be saved on a central server owned by HIPPA-compliant CommCare and UConn Microsoft Azure Cloud until it has been securely transferred to our computers. All research data will be stored in the double-locked research offices within the Clinical and Community Research Program within the Yale University AIDS Program. Client level data will be stored with the research study number and without any unique identifiers. All identifiers that link study number to study subject will be housed in PGP encrypted, password-

protected computers available only to the Data Manager/Statistician, Project Director and the Principal Investigator.
Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

The data will be stored in the manner noted above for at least seven years after completion of the study. All confidential information (study instruments, pharmacy record, etc.) , collected in paper format, willbe recorded with the study participant number only and maintained in locked cabinets within our offices at the Yale University AIDS Program and will only be available to be opened by the Data Manager, Project Director or the Principal Investigator. Data collected from online platforms such as CommCare and saved in soft copy format will be stored in the Yale shared folder (J drive). Only the Data Manager, Project Director, the PI, and Co-Is, with valid Yale NetIDs and special permission from the Yale administrator, will have access to this data. With the guidance of the Yale University Information Technology Services and HIPAA departments, data will be destroyed to ensure proper methodology is used when shredding files and deleting computer files. In addition, all the text messages will be "shredded" using PGP Desktop Shred which removes all traces of the file on the computer.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The Principal Investigator, Co-Investigator, and research staff will have access to the data.

Dr. Yerina Ranjit, Assistant Professor in the Department of Communication at the University of Missouri Columbia, will also have access to the data. University of Missouri, Columbia is a site that will be relying on Yale IRB review for the limited engagement of Dr. Ranjit for obtaining identifiable data.

g. If appropriate, has a Certificate of Confidentiality been obtained?

Yes, the Certificate of Confidentiality from National Institute on Drug Abuse (NIDA) has been obtained on May 22, 2017.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

Attempts to harm oneself or someone else will be reported to the proper authorities.

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