Health and Justice: A Continuum of Care for HIV and SU for Justice-Involved Young Adults (PHASE 2)

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Study Protocol and Statistical Analysis Plan

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Health and Justice: A Continuum of Care for HIV and SU for Justice-involved Youth (R01 DA 043122)

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Project Overview

Statement of Responsibility for developing and executing DSMP

The Principal Investigator accepts full responsibility for the development and execution of this Data and Safety Monitoring Plan.

Brief protocol description and study design

This protocol concerns the adaptation, efficacy-testing and implementation evaluation of a multi-component service delivery model (Link2CARE) that aims to increase HIV/STI testing and substance use (SU) screening; reduce HIV and SU risk; and increase linkage to HIV, STI and SU services in justice involved youth (JIY) who are enrolled in an alternative sentencing program (Brooklyn Justice Initiatives; BJI). We propose to adapt and integrate the following evidence-based strategies to create Link2CARE: (i) **Screening:** Offer an onsite rapid oral HIV test and STI urine test at intake into BJI and screen HIV risk behavior and SU; (ii) **Brief intervention**: use brief interventions (1-2 sessions) to reduce HIV risk and SU behavior and promote treatment/service readiness *(MOVE*[1] and *NYSBIRT*[2,3]); (iii) **Linkage to HIV and SU care**: use a strengths-based patient navigator approach to mobilize JIY strengths and reduce barriers to treatment, while establishing formal relationships and referral protocols with service providers. We have initiated a partnership with BJI, which serves 9000 JIY annually, and Project STAY, a youth-focused, hospital- and community-based, health and HIV treatment program; Project STAY HIV testing outreach workers will be embedded into BJI to deliver Link2CARE. We will test the efficacy of Link2CARE in a randomized controlled trial among N=450 BJI-enrolled JIY (18-24 y.o.), randomized to either Link2CARE or standard of care (SOC) and conduct implementation evaluation to explore individual-, staff, and system-level influences on implementation of this new model to inform scale-up and dissemination. Youth will be assessed at baseline and 3-, 6-, and 12-months post-intervention. BJI and Project STAY staff will be assessed before launch of Link2CARE and 12 and 24 months later.

Study aims and primary and secondary outcomes

The study has three aims.

1. Among 450 (18-24 y.o) JIY in BJI randomized to either Link2CARE or standard of care (SOC), to determine ***the efficacy of Link2CARE*** delivered by STAY staff embedded within BJI on (a) HIV outcomes: HIV testing/repeat testing; HIV risk behaviors; (b) STI outcomes: STI testing/repeat testing; linkage to care of JIY with STIs; (c) SU outcomes: SU screening; SU; linkage to care of JIY with SU/D; and (d) (exploratory) linkage to care of HIV+ youth and linkage to PrEP for (behaviorally) eligible HIV– youth.

2. To determine ***the influence of theoretically-based mechanisms of change*** **of Link2CARE** (e.g., predisposing characteristics, enabling resources, perceived need, organizational climate; staff attitudes) on the proposed HIV, STI and SU outcomes.

3. To describe Link2CARE implementation and elucidate the ***system/organizational-, staff-, and youth-level factors that influence implementation (i.e. acceptability, sustainability, feasibility*** ***of Link2CARE in an ASP*** to develop a plan for dissemination and scale-up of Link2CARE in New York City

The study has the following primary, secondary, and exploratory outcomes (related to aim 1)

*Domain 1 (**primary outcomes**: HIV outcomes)*: (a) total number of unprotected anal and vaginal sex occasions in past three months at 12 month FU; (b) acceptance of HIV testing at initial offering (y/n), (c) any HIV

testing between 6-month and 12-month FU (y/n).

*Domain 2 (**secondary outcomes:** SU outcomes):* (a) frequency of youth substance use in past 30 days at 3-, 6- and 12-month FUs; (b) number of youth referred to SU treatment at 3-, 6- and 12-month FUs; at (c) number of youth attending intake plus one treatment session at 3-, 6- and 12-month FUs.

*Domain 3 (**secondary outcomes:** STI testing outcomes):* a) acceptance of STI testing at initial offering (y/n), (b) any STI testing between 6-month and 12-month follow up; (c) number of STI+ youth referred to STI treatment at 3, 6, and 12 months FUs; (d) number of STI+ youth attending ≥1 treatment appointment at 3, 6, 12 months FUs.

*Domain 4 (**exploratory outcomes**: HIV/PrEP linkage outcomes):* (a) number of HIV+ youth referred to HIV treatment at 3, 6, and 12 months FUs, (b) number of HIV+ youth attending at least one treatment appointment at 3, 6, and 12 months FUs; (c) number of youth behaviorally PrEP eligible referred to PrEP/medical care at 3, 6, and 12 months FUs, (b) number of youth behaviorally PrEP eligible attending at least one HIV care appointment care at 3, 6, and 12 months FUs.

TRIAL MANAGEMENT

Study/data collection sites

Data will be collected at **Brooklyn Justice Initiative (BJI), run by Center for Court Innovation**. BJI is an alternative sentencing program (ASP) for JIY processed through Brooklyn Criminal Court. BJI aims to reduce re-offending and increase public safety; promote use of meaningful social services; provide rigorous compliance monitoring; and reduce criminal convictions and use of jail. Located in the Brooklyn Criminal Courthouse, BJI serves 9,000 youth/year; almost all (94%) are mandated to BJI for ≤15 days.

Study sample description

To address the study aims we will collect data from a sample of youth aged 18-24 who have been placed in BJI (sample 1), from a sample of HIV testing outreach staff (sample 2) and from staff at BJI (Sample 3).

Sample size and power

The total sample size of sample 1 will comprise N=472 youth currently enrolled at BJI: n=14 youth will serve on an advisory panel to provide feedback as MOVE and NYSBIRT are adapted; n=8 youth will pilot test the adapted Link2CARE protocols prior to the efficacy test of Link2CARE; and n=450 youth will be randomly assigned (1:1) to either Link2CARE or standard of care. Sample 2 will comprise N=2 Project STAY outreach workers who will be embedded at BJI and will deliver all elements of Link2CARE to youth. Sample 3 sample size is expected to be all 15 staff who work at BJI.

Based on our previous work, the retention rate for studies of JYI was about 75% to 80%. Even though we anticipate being able to maintain 20% attrition, we conservatively use 25% attrition at 12-month FU in this power calculation. Under such assumptions and with a baseline sample of 450 participants, we estimate a final sample of at least n=338 with complete data for the primary analysis at 12-month FU. With 169 participants per group and the use of Bonferroni correction, we will be able to provide 80% power to detect a standardized effect size of .35 or more on any of the three primary outcomes (i.e., total number of unprotected anal and vaginal sex occasions in past three months, acceptance of HIV testing at initial offering; and frequency of substance use in past 30 days). The standardized effect size of .35 is considered as a relatively small to moderate effect size according to Cohen[4] and our previous study suggests that it is an achievable effect. A substantial increase in sample size will not strongly impact effect size – e.g. to reduce the standardized effect size from .35 to .32, 100 more participants (22% increase in current sample size) would be required. Even if actual attrition is greater than expected e.g. say 30%, the detectable standardized effect size will only increase slightly to .36. Furthermore, as we will impute missing data using informative covariates for the primary analyses and using a less conservative Holm procedure for multiple comparison adjustment, power to detect such effects will actually be greater than 80%.

Table 1. Inclusion/exclusion criteria

Study Phase	Study Sample	Inclusion Criteria	Exclusion Criteria
Phase 1: **Adaptation for Link2CARE**	Peer advisory panel n=14	1) Between 18-24 years of age 2) Currently enrolled in BJI 3) Conversant in English (in the past two years, only two JIY at BJI have required language assistance).	1) Medical or psychiatric illness requiring hospitalization 2) Serious suicidal or homicidal ideation
	BJI staff n=6	1) Currently employed at BJI	None
	Pilot Youth n=8	1) Between 18-24 years of age 2) Currently enrolled in BJI 3) Conversant in English (in the past two years, only two JIY at BJI have required language assistance).	1) Medical or psychiatric illness requiring hospitalization 2) Serious suicidal or homicidal ideation
Phase 2: **Link2CARE Efficacy Trial and Implementation Evaluation**	Youth n=450	1) Between 18-24 years of age 2) Currently enrolled in BJI 3) Engaged in any unprotected sexual activity (lifetime), 4) Conversant in English (in the past two years, only two JIY at BJI have required language assistance).	1) Medical or psychiatric illness requiring hospitalization 2) Serious suicidal or homicidal ideation 3) HIV+ status by self-report and linked to care
	Project STAY staff n=2	1) Currently employed Project STAY and involved in delivering Link2CARE.	None
	BJI staff n=15	1) Currently employed at BJI	None

Target population distribution

Inclusion of Women. There is no inclusion or exclusion of participants based on gender. Based on demographic data from the Brooklyn Justice Initiative, we anticipate females will comprise 28% of the youth sample, representing the demographics of the justice system nationwide.

Inclusion of Minorities. We will not exclude participants based on ethnicity. The majority of youth enrolled in the Brooklyn Justice Initiative are minority (56% African American, 18% Hispanic), representing the demographics of the justice system nationwide.

Children: The proposed study does not include children aged 18 or younger. The application proposes to develop a screening, brief intervention and linkage-to-care service delivery model that targets those at significant risk for HIV and SU. In the US, youth age 18-24 carry the burden of HIV and substance use problems compared to youth younger than 18. Moreover, the development of a linkage-to-care program for youth younger than 18 would have to involve caregivers who can provide consent for youth to receive both SU and HIV treatment. Involvement of caregivers would necessitate a different linkage-to-care intervention, which is beyond the scope of the proposed study.

Project Timeline

TABLE 2: Projected Timetable

	Year 1		Year 2		Year 3		Year 4		Year 5	
Months	1 – 6	7 – 12	13 – 18	19 – 24	25 – 30	31 – 36	37 – 42	43 – 48	49 – 54	54 – 60
Adaptation and pilot testing of MOVE and NSYBIRT										
Train staff										
Recruit JIY										
Implement Link2CARE										
JIY assessment (3-month)										
JIY assessment (6-month)										
JIY assessment (12-month; main outcomes)										
Staff assessments (implementation outcomes)										

Acknowledgment permission requirement

The PIs acknowledge the requirement to request and receive permission from the PO for protocol or DSMP changes in advance of their implementation.

DATA MANAGEMENT AND ANALYSIS

Data acquisition, entry and transmission

Study data will be collected in Phases 1 and 2. All Phase 1 and all baseline assessments (Phase 2) will be collected at BJI. Subsequent Phase 2 assessments will occur at BJI, in the participant's home or at another agreed upon location. Note: BJI is not involved in survey administration, data entry and management, or data storage.

Phase 1: Advisory Panel data: Peer (n=14) and Staff (n=6) Advisory Panels will meet in a series of Panel workgroups during Phase 1 to provide feedback on the adaption of the SU and HIV interventions. Data from these Panel workgroups will be gathered in note form by work group facilitators and will not contain any participant identifying information. These data will be transcribed by research assistants and will be used between workgroups to inform adaptation of interventions.

Pilot data: n=8 youth who participate in a pilot of the SU and HIV protocols will complete paper-and-pencil process measures following the completion of the pilot which will be administered by human subject-trained research assistants (RAs). These research assistants will bring completed questionnaires to the research offices at NYSPI on the day of data collection. These data will be entered in an electronic database by human subject-trained research assistants. This database will be stored on password-protected computers in encrypted files. Researchers will retain the pilot process assessments until the completion of all project activities in Year Five when they will be destroyed following HIPAA standard document destruction services.

Phase 2: Substance use and HIV behavioral risk screen. Following randomization and baseline assessments, n=225 JIY randomized to Link2CARE will complete substance use and HIV behavioral risk screeners. Screening will take place at BJI in private rooms or other agreed upon location (for follow-up survey assessments). Data will be captured on encrypted, password protected computers, entered directly by human subjects-trained RA's into CiW using Sawtooth Software. Sawtooth Software allows for all standard question types, skip patterns, and data piping. Web-based data collection will ***not*** be used. Following interview completion, RAs will then transport interview data to NYSPI in the encrypted password protected computer, and immediately upload it upon return into the master database at NYSPI held on a secure server.

HIV and STI testing: Following randomization and baseline assessment, all youth will be offered an HIV and an STI test for Chlamydia and gonorrhea; initial testing will take place onsite at BJI. All youth will also be offered HIV and STI testing at each follow-up interview (3m, 6m and 12m). ***HIV testing*** will be done using Oraquick advance rapid HIV test. Following brief pre-test counseling, an oral swab will be used to collect saliva to conduct HIV rapid test. Once conducted, the embedded Project STAY staff member (LINK2CARE condition) or human subjects-trained RA (standard of care) will provide results to the participant and HIV+ JIY will be immediately linked to care following Link2CARE linkage protocols. The Project STAY staff or RA will then place the swab in a closed Developer Solution vial, then back into the package. The entire package will be placed in a baggie. The baggie with the used test will be brought back to NYSPI by human-subjects trained RAs and turned in to the Project Director who will enter the results into a the project database at NYSPI that is held on a secure server. The baggie containing the used OraQuick test and materials will then be disposed of in the appropriate waste container. Staff (interviewers and office staff) will wear gloves when manipulating test materials. ***STI testing*** will occur by the collection and processing of the urine specimens using a Gen-probe APTIMA Urine Specimen Collection Kit for Male and Female Urine Specimens. The testing kits are provided and the urinalysis will be performed by the New York City Department of Health (NYCDOH) at no cost as part of an ongoing agreement with Project STAY. The client is instructed about how to provide the urine sample, and is sent to the bathroom by either the embedded Project STAY staff member (LINK2CARE condition) or human subjects-trained RA (standard of care). Upon return, the Project STAY staff member or RA packages the sample and arranges for pickup by the Department of Health's (DOH) Bureau of STD control. NYCDOH uses the third generation nucleic acid amplification test (NAAT), yielding qualitative testing results. Specimens will be collected and transferred into their respective specimen transport tubes. The transport solutions in these tubes release the rRNA targets and protect them from degradation during storage. When the APTIMA Combo 2 Assay is performed in the laboratory, the target rRNA molecules are isolated from specimens by the use of capture oligomers in a method called target capture. After the target capture steps are completed, the specimens are ready for amplification. The GEN-PROBE APTIMA Combo 2 Assay replicates a specific region of the 23S rRNA from CT and a specific region of the 16S rRNA from GC via DNA intermediates. A unique set of primers is used for each target molecule. Differences in the kinetic profiles of the CT and GC labeled probes allow for the differentiation of signal; kinetic profiles are derived from measurements of photon output during the detection read time. The chemiluminescent detection reaction for CT signal has very rapid kinetics and has the "flasher" kinetic type, while the detection reaction for GC signal is relatively slower and has the "glower" kinetic type. Assay results are determined by a cut-off based on the total RLU and the kinetic curve type. Written documentation of the test results will be obtained by the research office from the NYCDOH Microbiology laboratory within 7 days after the urine sample was delivered. The Project Director who will enter the results into a the project database at NYSPI that is held on a secure server Respondents randomized to Link2CARE who test positive will be informed by embedded Project STAY staff of their results and will immediately be linked to care by STAY staff following Link2CARE linkage protocols. Respondents randomized to SOC who test positive will be contacted by study staff using a succession of methods (telephone, registered letter, and, if refused or undelivered, regular mail). Participants will be informed that antibiotics are used to treat Chlamydia and Gonorrhea. We will counsel that all sex partners within the last 60 days should be evaluated and treated and to avoid sex until they and their partners have been treated for at least 7 days or 7 days after a single dose treatment. Specific referral procedures will be followed to maximize chances that participants will seek treatment.

Face-to-face survey interviews - youth. Phase 2 youth survey interviews will be completed at baseline, 3m, 6m, and 12 months post baseline with n=450 youth. Interviews will take place at BJI in private rooms or other agreed upon location (for follow-up survey assessments). Data will be captured on encrypted,

password protected computers, entered directly by human subjects-trained RA's into CiW using Sawtooth Software. Sawtooth Software allows for all standard question types, skip patterns, and data piping. Web-based data collection will ***not*** be used. Following interview completion, RAs will then transport interview data to NYSPI in the encrypted password protected computer, and immediately upload it upon return into the master database at NYSPI held on a secure server.

Face-to-face survey interviews - staff. Phase 2 staff survey interviews will be completed pre-implementation of Link2CARE, at 12m (during implementation of Link2CARE and at 24m (post-implementation of Link2CARE) with n=15 BJI staff and n=2 embedded Project STAY staff. Interviews will take place at BJI in private rooms. Data will be captured on encrypted, password protected computers, entered directly by human subjects-trained RA's into CiW using Sawtooth Software. Sawtooth Software allows for all standard question types, skip patterns, and data piping. Web-based data collection will ***not*** be used. Following interview completion, RAs will then transport interview data to NYSPI in the encrypted password protected computer, and immediately upload it upon return into the master database at NYSPI held on a secure server.

Post-implementation focus group. Project STAY and BJI staff will participate in a one-time focus group following the implementation of Link2CARE, which will take place in a private room at BJI. The focus group will be digitally recorded, transported by RAs in a locked pouch back to NYSPI and uploaded onto a secure server at NYSPI. The recordings will then be transcribed for analysis. These recordings will be retained until the completion of all project activities in Year Five when they will be destroyed following HIPAA standard document destruction services.

Data analysis plan

Intent-to-treat principles will be invoked in the primary analysis. The primary aim is to determine whether participants randomized to Link2CARE show greater improvement in HIV outcomes from baseline to 12-month follow up than participants in SOC. Measurement of primary HIV outcomes includes three variables: number of unprotected sex occasions, whether participants accept HIV testing at initial offering (y/n), and any (repeat) HIV testing between 6-month and 12-month follow up (y/n). Other behavioral and linkage variables to be examined as secondary and exploratory outcomes are described in Section 3.3.9.3. Implementation outcomes to be examined include feasibility, acceptability, and sustainability. In addition, we will examine potential CFIR correlates of implementation, such as organization culture and climate and staff attitudes. Finally, mediators associated with service use as specified by the Andersen model will be examined, including motivation for treatment, perceived barriers to treatment, prior service utilization.

Analysis plan for Specific Aim **1.** Prior to conducting our multivariable analyses, we will examine study variables using descriptive statistics, testing for differences across demographic characteristics (e.g., race/ethnicity, age) using t-tests, ANOVAs, and Chi-squares, as appropriate. Systematic baseline differences are not expected; however, any parameters that differ across conditions at baseline will be included as covariates in subsequent models. We will calculate descriptive summary statistics corresponding to study variables at each follow-up (FU) to understand any temporal patterns, as well as compare the two groups in terms of average change from baseline to 12-months post-baseline. We will use the general framework of generalized linear models (GLM) to model the longitudinal outcome trajectories and GEE method to account for within-subject correlation across the four time points (baseline, 3-, 6-, and 12-months). Stratified randomization of participants to the groups based on their gender requires that the analysis also include gender as covariate. The general form of the analysis model will be $g(\mu)=\alpha_0+\alpha_1 X+\beta I+\sum\gamma_i T_i+\sum\delta_i T_i I$, where g denotes the link function (identity for continuous outcome, logit for binary outcome and natural log for count outcomes) X represents the indicator of female (vs. male), I is the group indicator for Link2CARE (vs. SOC), and T_i is the indicator for time at 3-month, 6-month, and 12-month evaluation (vs. baseline) for i=1, 2, and 3. The interaction coefficients δ_i are of interest, measuring the difference in the rate of change in outcome across the two treatment groups at each follow-up assessment. We will employ the above analytic approach to examine differences between youth in Link2CARE and in the SOC condition with respect to key study parameters within these four domains detailed below. *Proposed hypotheses* are that the experimental arm (Link2CARE) would have better outcomes (e.g. greater reduction on total number of unprotected anal and vaginal sex occasions in past three months from baseline to 12 month FU; greater increase in proportion of acceptance of HIV testing at initial offering; greater reduction on frequency of substance use in past 30 days at 3-, 6- and 12-month FUs; and of those referred to SU treatment, a greater number of youth attending intake plus one treatment session at 3-, 6- and 12-month FUs)

compared to the standard of care; all hypothesis tests will be conducted under the control of familywise error rate no greater than 0.05 level. The Holm step down procedure will be employed to adjust for multiple comparisons.

1. *Domain 1 (**primary outcomes**: HIV outcomes)*: (a) total number of unprotected anal and vaginal sex occasions in past three months at 12 month FU; (b) acceptance of HIV testing at initial offering (y/n), (c) any HIV testing between 6-month and 12-month FU (y/n).
2. *Domain 2 (SU outcomes):* (a) frequency of youth substance use in past 30 days at 3-, 6- and 12-month FUs; (b) number of youth referred to SU treatment at 3-, 6- and 12-month FUs; at (c) number of youth attending intake plus one treatment session at 3-, 6- and 12-month FUs.
3. *Domain 3 (**exploratory outcomes**: HIV/PrEP linkage outcomes):* (a) number of HIV+ youth referred to HIV treatment at 3, 6, and 12 months FUs, (b) number of HIV+ youth attending at least one treatment appointment at 3, 6, and 12 months FUs; (c) number of youth behaviorally PrEP eligible referred to PrEP/medical care at 3, 6, and 12 months FUs, (b) number of youth behaviorally PrEP eligible attending at least one HIV care appointment care at 3, 6, and 12 months FUs.
4. *Domain 4 (STI testing outcomes):* a) acceptance of STI testing at initial offering (y/n), (b) any STI testing between 6-month and 12-month follow up; (c) number of STI+ youth referred to STI treatment at 3, 6, and 12 months FUs; (d) number of STI+ youth attending ≥1 treatment appointment at 3, 6, 12 months FUs.

Analysis plan for Specific Aims 2 and 3**.** Descriptive statistics will be computed to quantify implementation at every step, by participant and by provider. Thus, we will be able to compute uptake of LINK2CARE, dose/intensity of intervention received, number of providers delivering each intervention, and other implementation parameters. Of note for Aim 2, which seeks to examine the proposed mechanisms of change of the intervention on HIV, STI and substance use outcomes, a given outcome (e.g. HIV/STI testing uptake, or PrEP uptake or reduced substance use) of this analysis will only be examined among those for whom it is relevant. For example, if a youth does not meet criteria for PreP and as such is not offered PrEP, we would not include this youth in analyses of mechanisms of change of Link2CARE as they influence substance use or PrEP uptake as an outcome. We will examine the changes in specific outcomes (e.g. sexual behavior post-intervention) as a function of proposed theory-based intervention mediators (e.g. predisposing characteristics, enabling resources, perceived need for treatment/services). We will use structural equation models for these analyses. Structural equation modeling is preferred to multiple regression techniques because of the potential measurement error in our mediating variables and because of the possible feedback between dependent and mediating variables. We will test the model described in Figure 1 in the application, entering intervention condition as exogenous variables and the mediating factors included in Figure 1 as endogenous variables. Prior to conducting the structural analyses, however, we will examine the effects of the intervention on the putative mediating variables; a condition for inclusion in the equation will be a significant intervention effect on the potential mediators. Using standardized path coefficients, we will examine the relative associations of mediators to behavior change. We will also examine the path coefficient for the direct effect of the intervention after removing the effects of mediating constructs. For example, Link2CARE may have a more positive effect on acceptance of HIV (and STI) testing among JIY with greater perceived HIV risk, greater motivation to receive services, or positive HIV-testing history. Similarly, Link2CARE may have more positive effect on linkage outcomes when operating in an ASP that is more supportive of concepts perceived as innovative by both BIJ and STAY staff. Here, organizational culture would appear to modify Link2CARE's impact on youth service referral and engagement outcomes. We will examine the Lagrange Multiplier and Wald Tests to consider the deletion or inclusion of paths[5]; ultimately, however, deletion or inclusion of paths will be informed by theoretical underpinnings. Once the model is identified, we will test for group differences between intervention conditions in latent constructs and in the proposed paths between these constructs. This method will allow us to estimate the intervention effects on the constructs directly as well as their relationships to one another.[6] We will use three goodness-of-fit indices: Bentler-Bonnet's Normed Fit Index, Bentler-Bonnet's Non-Normed Fit Index, and the Comparative Fit Index. We will also verify the root mean-square error of approximation (RMSEA) as an index of misfit. Well-fitting models will have fit indices of.90 or higher and <.06 for RMSEA.

Analysis of participant attrition and missing data. We will make every effort to retain participants in the study to avoid bias due to attrition. For those individuals who refuse continued participation, we will document reasons for study discontinuation and Rubin's multiple imputation method with 11 repeated imputations will be

employed to impute the missing endpoint for conducting the intent-to-treat analysis.

QUALITY ASSURANCE

Procedures in place to ensure the validity and integrity of the data

All data collection protocols include a form on which research staff members record any problems with the data collection or unusual occurrences during the collection. They also are encouraged to bring problems to the attention of the Project Director, or PI. These members of the research staff also meet on a regular basis to identify and address any issues that arise. These procedures allow our research staff an opportunity to quickly review and respond to any possible concerns. We expect missing data to be minimal, nevertheless regular (quarterly) quality assurance checks will be made by the Project Director to identify any systematic missing information and remedies will be enacted.

Procedures to guarantee the accuracy and completeness of the data, during data collection, entry, transmission, and analysis.

To check for errors in data entry, we will adhere to the following protocol. All face-to-face surveys will be recorded. One out of every seven recordings for each interviewer will be compared to the entered interview. If we identify a proportion of errors that is more than 1% error, we will temporarily suspend the interviewer from active interviewing. We will listen to all interviews for comparison purposes, identifying any errors and will re-train the interviewer to ensure accuracy and completeness of all face-to-face survey interviews. A subset (10%) of all data from hard-copy/paper-pencil instruments that is entered into the project database will be similarly checked. If we identify a proportion of errors that is more than 1% error, we will reenter all questionnaires and subsequently compare both data sets. We will go back to the original surveys to resolve all inconsistencies. To prevent data entry problems we will prepare a data entry system that will alert us when data are entered that are out of range.

Procedures for preventing and addressing breaches of confidentiality

Above we described how data are protected during collection and transportation. Once at NYSPI, all data will be saved on secure, password-protected servers. The information gathered will be used only for scientific, educational, or instructional purposes. All interviewers and all other study staff are trained on the importance of subject confidentiality.

REGULATORY ISSUES

Procedures for research team management of AEs, SAEs and other study risks such as mandatory reporting requirements (e.g., child abuse, infectious disease, etc.)

The Principal Investigator, Dr. Elkington has the ultimate responsibility for reviewing conduct of the study and data produced from it, including the reporting of any adverse events to the respective IRBs.

AEs and SAE that come to the attention of any staff person involved in the study, have to be reported directly to the PI using an *Adverse Event Report Form*. If no action has yet been taken, the PI ensures that these events are addressed by the timely intervention of either herself, Dr. Cohall or one of the Project STAY staff at BJI. The PI furthermore ensures that the respective IRBs are informed, in line with the seriousness of the event. And follows NYSPI IRB protocol to report (S)AEs and receives feedback about appropriate course of action to follow. Below is a table of potential AEs and SAEs and the proposed procedures to detect them.

Procedures to prevent the violation of confidentiality in accordance with reporting requirements are limited by the mandatory nature of these requirements. Therefore, all subjects are informed in the consent document that the only times other people will find out what they said during the study are: (1) If they describe the physically or sexually abusing a child. This will be reported to the New York State Central Registry (NSCR) which takes calls for child abuse and neglect allegations. If accepted, the NSCR will forward to Bronx field office for the City's Administration for Children's Services (ACS). (2) If they say they want to harm themselves or another person, the researchers can break confidentiality to refer them for further evaluation. (3) In cases of a positive HIV or STI diagnosis, we will follow standard procedures, in line with legal requirements. The mandate for HIV is for the provider doing posttest counseling is to assess for partner notification within 30 days of diagnosis. This will be handled by Project STAY staff or staff from the specific clinic the youth has been

linked to if not project STAY. Patients will be asked if they can contact sexual partners themselves. If not, sexual partners can be brought in by the patient and clinic staff notifies partners. The third option is to inform the New York City Department of Health and Mental Hygiene (DOHMH), which does anonymous notification and advices sexual partners to go to their physician and get tested. The assessment for partner notification includes a check for domestic abuse risk. For other STIs, partner notification is voluntary not mandatory but Project STAY staff will assess for partner notification and ask the patient to notify partners themselves, the patient can bring partner in, DOHMH can assign a field worker for anonymous notification; Project STAY staff will never call the partner down. All STI, including Chlamydia, Gonorrhea and HIV require an individual, identified report to the city as they occur; this is a direct online report into the DOHMH website.

Table 3 Potential AEs and SAEs and the proposed procedures to detect them.

Types/Categories of Events Anticipated (whether or not occurred)	***Procedure to detect***
Extreme psychological distress in participants	• General follow-up and check-in with all participants during and following each scheduled baseline, 3, 6- and 12-month interviews (Phase 2). • Check-in and debriefing with participants following each HIV/STI testing occasion; pre- and post-interview question "scale 1-10, how do you feel…" • Check-in with provider at 3, 6- and 12-month interviews (Phase 2).
Negative feedback from participant upon debriefing (e.g., thought participation might be harmful or upsetting to others)	
Suicidality (thoughts or intentions)	
Homicidality	
Suspicion of safety concerns in the home	
Increase in sexual risk behaviors or substance use	
Increase in conflict/distress between participants and partners	
Youth detention/incarceration	
Non-voluntary Disclosure of HIV or STI diagnosis	
Non-adherence to treatment and care for HIV+ or STI+ youth	
Loss of Confidentiality	

Staff training (including NIH-required human subjects training and other related training)
All staff involved in the study (researchers, clinic staff, the Implementation Coach, the Youth Outreach Worker) has successfully completed a mandatory, training/testing program on human subject protection; staff is required to keep their ethics certification up to date. In addition, clinic staff are trained in issues related to ethnic and cultural diversity and to concerns and needs of the adolescents they will interview and in procedures for addressing any problems that may arise. Furthermore, research and program staff are trained to identify events that would fall under mandatory reporting guidelines, to respond to distress and in emergency procedures that are activated if an adolescent admits to thoughts of harming himself or others. The Program furthermore contains specific training activities to ensure skillful implementation of activities in line with ethical guidelines, e.g., Peer Navigators will be thoroughly trained on the imperative of confidentiality and other ethical aspects of being a peer navigator.

Certificate of confidentiality
A Certificate of Confidentiality will be obtained from NIH to protect the privacy of our research subjects by protecting the research team and our institutions from being compelled to release information that could be used to identify subjects with a research project.

Procedures and timeline for reporting AEs and SAEs to NIDA
Adverse Events (AEs) will be reported to the NIDA PO at least once per year as part of the annual progress report. This report will describe the event, when it occurred, the study arm of the participant, and the outcome/resolution. If there were no AEs, we will include a statement in the progress report that no AEs occurred. In case of SAEs, the contact PI will ensure that they will be reported to the NIDA PO within 24 hours by email and that a written report is submitted to the PO no more than two days later.

Reporting of IRB actions to NIDA
Any IRB actions that negatively impact the implementation of the study will be will be reported to the NIDA PO within 24 hours by email.

Acknowledgment permission requirement
The PIs acknowledge the requirement to request and receive permission from the PO for protocol or DSMP changes in advance of their implementation.

Trial Stopping Rules
Only two of the three co-primary endpoints will be monitored for early stopping: (1) total number of unprotected anal and vaginal sex occasions in past three months at 12 month FU; (2) any HIV testing between 6-month and 12-month FU (y/n). We will follow a modified Haybittle-Peto rule[7] to propose early stopping as follows: the z-score for testing the null hypothesis for each of the two primary outcomes will be calculated once during interim analyses (see below) when one-quarter of the expected total 12-month outcome data has been observed (after approximately 6-months of 12-month data collection). This will allow the PSMB to recommend continuing to recruit subjects or stop the trial for strong positive or negative efficacy prior to the end of subject recruitment.

The z-score for early stopping will be $Z = 3.6623$ for either monitored outcome, corresponding to a normal two-tailed critical value cutting off nominal probability 0.00025 in each tail. It follows that either endpoint may suggest early stopping with total two-tailed probability 0.0005 under the null hypothesis and therefore the probability of early stopping under the null hypothesis for either endpoint in either direction will be no greater than 0.001. This stopping rule is less conservative than an O'Brien-Fleming-like alpha spending function monitoring plan, yet is still sufficiently conservative to leave the terminal significance criteria nearly unaffected. In particular, assuming no early stopping, if either of the two monitored co-primary endpoints specified above possesses the smallest *P*-value among all three co-primary endpoints, the group comparison will be declared significant at the 0.05 level (adjusted for multiple comparisons) if the terminal z-score criterion is $Z = 2.3978$ or greater. This *Z*-score is very close to the nominal $0.05/3 \approx 0.01667$ two-tailed normal critical value of 2.3940, which is the initial required criterion under the Holm step-down procedure without sequential monitoring. If the unmonitored co-primary endpoint (acceptance of HIV testing at initial offering, y/n) should have its *P*-value as smallest and less than or equal to $0.05/3 \approx 0.01667$, then it will be declared significant (at the two-tailed 0.05 level, adjusted for multiple comparisons).

Assuming no early stopping and with neither of the two preceding possibilities occurring at terminal analysis, testing stops under the Holm step-down procedure and none of the three null hypotheses will be rejected. Assuming no early stopping but with one of the two preceding possibilities occurring at terminal analysis, the next step in the Holm step-down procedure will use either the nominal *P*-value for the unmonitored co-primary endpoint (if it has the second smallest *P*-value) or, if not, the *P*-value for the monitored endpoint with the second smallest *P*-value *adjusted for the interim analysis.* This *P*-value will again be very close to the nominal *P*-value due to use of the conservative modified Haybittle-Peto stopping boundary. The appropriate two-tailed *P*-value must equal $0.05/2 = 0.025$ or less to declare significance; if not, testing stops and only the first endpoint result will be reported as significant. If so, then testing proceeds under the Holm step-down procedure to the remaining endpoint with criterion *P*-value 0.05, unadjusted if for the unmonitored endpoint or adjusted for interim monitoring if for one of the monitored endpoints. If the 0.05 *P*-value criterion is not achieved, only the preceding two endpoints will be declared significant. If the 0.05 *P*-value criterion is achieved, all three endpoints will be declared significant at the 0.05 level (adjusted for multiple comparisons).

The analyses on the two primary endpoints will be presented to the PSMB (see Efficacy Data below) in a blinded fashion (i.e. A vs B) with a brief description as to whether or not we meet the stopping rule. Of course, the PSMB may request additional information and/or unblinding on a need-to-know basis. Other reasons for stopping the trial, e.g., unexpectedly low recruitment or poor retention, will be considered by the PSMB during their regular pooled-data reviews at six-month intervals. The PSMB has substantial experience with oversight of trial integrity issues and will come to a recommendation around stopping related to poor enrollment or

retention issues as necessary. Prior to the start of the trial we will propose recruitment and retention benchmarks for their review and approval.

TRIAL SAFETY

Potential risks and benefits for participants

The benefits of this study include gaining knowledge that may be fundamental to improving the continuum of HIV and SU care for JIY and developing innovative models of service delivery to a highly vulnerable population. There are very few programs designed to screen, reduce risk and link to HIV and SU care for JIY, most are developed for adults and do not take into consideration developmental needs of the youth. A screening, risk reduction and linkage model that addresses organizational and staff level- barriers to linkage and engagement, as well as directly targeting youth-level barriers to reducing risk behavior and service uptake is critical to providing JIY with skills necessary to navigate multiple systems (substance use treatment, HIV care and justice system), remove barriers to service use, enroll in and remain in services. The fact that rates of HIV are elevated in correctional populations compared to the general population, targeting youth who are attending community programs in lieu of jail or detention represents a critical point for intervention. Moreover, substance use/disorder in JIY are much higher than youth in the general population, and that these youth have much worse outcomes associated with substance use but receive services at much lower rates warrants immediate attention. This study will provide an opportunity to improve identification, risk reduction and enrollment in care for youth who are at the highest risk of HIV and substance use, yet least likely to receive services. For these reasons, this study has the potential to impact the health and functioning of high-risk youth. Additionally, JIY will be asked specifically for their experience with the operation of Link2CARE in their agency and input into how to improve linkage to HIV substance use services for JIY. Study participants often derive a sense of altruism, accomplishment, and contribution to furthering understanding of the problem through their participation, and past participants in similar studies by the PI, co-Is and consultants have indicated the process was enjoyable and beneficial.

The importance of Knowledge to be gained

Prevalence of HIV and substance use disorders among JIY is significantly higher compared to youth in the general population. Ultimately, a study of this kind has the potential to (a) improve the outcomes for youth by detecting HIV risk, infection and problematic substance use, reducing risky behaviors and linking high risk youth to necessary care and treatment, while overcoming system and youth level-barriers to this process; and (b) identify multilevel factors that are associated with adopting and sustaining innovative practices. Risks to participation in the study (discussed above in the section 5.2) are reasonable given the importance of knowledge expected from the study.

TRIAL EFFICACY

Responsibility for data and safety monitoring

The project will use the Performance and Safety Monitoring Board (PSMB) of the HIV Center for Clinical and Behavioral Studies (P30-MH43520) at the New York State Psychiatric Institute. The HIV Center's PSMB is an external advisory group comprising community and clinical psychologists, a biostatistician, an ethicist, and a clinician not affiliated with HIV Center research projects or our home institutions. This PSMB has specifically been established to deal with studies focused on HIV infection and has the necessary expertise to address urgent issues that might arise in relation to the current protocol and to support us when protocol changes might be necessary. This PSMB, coordinated by the Statistics, Epidemiology, and Data Management (SED) Core of the HIV Center, monitors intervention projects associated with the Center on a yearly basis. The project will be reviewed at least once each year and more often if necessary or to follow up on PSMB recommendations. In addition, we will call on the PSMB as needed to address urgent matters that arise, including SAES/AEs, questions and concerns from the IRB, and discussions about possible protocol changes.

Composition of the PSMB

Bette Crigger, Ph.D. (Chair), Director of Ethics, American Medical Association, Chicago, IL.
Patricia Hawkins, Ph.D., Clinic Director, DC Community AIDS Network in Washington, DC

Joseph Hogan, Sc.D., Professor and Graduate Program Director, Department of Biostatistics and Co-Director, CFAR Outcomes and Biostatistics Core, Brown University, Providence, RI
Steven Morin, Ph.D., Emeritus Professor of Medicine, University of California, San Francisco, CA
Nina Regevik, M.D., Director, HIV Early Intervention Program, Raritan Bay Medical Center, Perth Amboy, NJ

Charge of the HIV Center PSMB
The PSMB is appointed by the HIV Center to ensure and maintain the scientific integrity of human subject research projects and to protect the safety of human subjects. The PSMB has the responsibility to assure the HIV Center that participants in research projects are not being exposed to unnecessary or unreasonable risks as a result of the pursuit of scientific objectives. The PSMB also assures the HIV Center that research projects involving human subjects maintain high standards of quality throughout the duration of these projects. The PSMB will review the study protocol and any protocol changes in relation to both the safety of participants and the overall scientific integrity of the project. Comments and recommendations will be directed to the Director of the HIV Center and to the Principal Investigators of the project.

Through the HIV Center Director or the SED Core Director, the PSMB has the authority to request summary reports, data listings, research documents, and any information determined to be necessary to fulfill its duties and responsibilities. The PSMB can request that the HIV Center Director obtains independent verification of some or all data relevant to the safety of human research participants and the scientific objectives of the trial. Independent verification may include examination of relevant medical and research records. Under extraordinary circumstances – for instance, continued failure on the part of an investigator to take appropriate measures for the protection of research participants from significant risk – the chair of the PSMB, with the agreement of the PSMB, can communicate directly with the Director of the funding agency.

Statement of no conflicts of interest
None of the members of the PSMB has an appointment at our institutions or research collaborations with the Principal Investigators or team.

Frequency of meetings
The PSMB typically meets on-site at the HIV Center at least once each year to monitor projects and through conference calls both among the board members and with the HIV Center leadership and investigators during the year to assure that PSMB recommendations are enacted. Regarding this specific protocol, the PSMB will meet as needed to address any of the above or other urgent or timely sensitive matters that might arise.

Plans for Interim Analysis of efficacy data
The aims of early interim analyses (in six-month intervals) are to (a) ensure that assumptions about mission-critical parameters (means, standard deviations, and prevalence of main outcomes) made for purposes of power are approximately correct; and (b) to monitor safety of the trial participants, reviewing all adverse events (AEs) and serious adverse events (SAEs). Interim analyses for safety and data monitoring of mission critical parameters, including recruitment and retention rates, will be conducted every 6 months by the trial statistician who will prepare the report for the PSMB (see Monitoring activities below). A third aim of interim analysis is (c) to check at a strategic point in the trial whether sufficiently strong evidence of positive or negative efficacy has accumulated to warrant consideration of stopping the trial (see Trial Stopping above). For all analyses the PI will remain blinded as to treatment assignments. As far as is feasible, the PSMB will also remain blinded, reviewing interim analyses prepared by the unblinded statistician in A/B format. They may, of course, request additional information for any safety concerns or risk-benefit analyses on an as-needed basis. Agreement on these procedures will be obtained with the PSMB prior to trial start. As described above, interim analyses for trial stopping will be conducted once after one-quarter of the 12-month data has been collected.

Monitoring activities
Although the Principal Investigator will have ultimate responsibility for reviewing conduct for the study and data emanating from it, including the reporting of any adverse events to the Institutional Review Boards of Columbia University/the New York State Psychiatric Institute (NYSPI) and NIDA, the PSMB will also review this project twice each year (every 6 months). The Principal Investigator will identify a list of adverse outcomes (e.g., significant psychological distress, loss of privacy) that might occur as a result of participation in the study. In

addition, in preparation for the presentation of the project to the PSMB, a blinded report will be sent to the PSMB members in the weeks before the meeting and include a 1) a brief description of the trial, 2) summary of progress to date, including participant baseline sociodemographic characteristics, 3) blinded data such as participant accrual and retention, prevalence of main outcomes, 4) a description of any AEs or SAEs, and 5) an interim efficacy comparison when one-quarter of the 12-month primary endpoints have been observed. Typically, this information is reviewed during the open session of the PSMB meeting. In closed session, the PSMB will review the data in blinded A versus B format (and, if needed, in unblinded fashion) after which, the PSMB members will present feedback to the project research team with respect to whether the study should be continued.

Communication Plan Acknowledgment of Reporting Requirement
The PIs acknowledge the requirement to report PSMB activity (meeting notes on the Board meeting, discussions, decisions, etc. pertaining to this project) as part of Annual Progress Report to NIDA.

REFERENCES

1. Wilson PA, al. e. Selection and Evaluation of Media for Behavioral Health Interventions Employing Critical Media Analysis. *Health Promotion Practice.* In press.
2. The National Center on Addiction and Substance Abuse at Columbia University. An SBIRT Implementation and process Change Manual for Practitioners https://www.centeronaddiction.org/sites/default/files/files/An-SBIRT-implementation-and-process-change-manual-for-practitioners.pdf [accessed 2/19/2016]; 2012.
3. Academic ED SBIRT Research Collaborative. The Impact of Screening, Brief Intervention, and Referral for Treatment on Emergency Department Patients' Alcohol Use. *Annals of Emergency Medicine*. 2007;50(6):699-710.
4. Cohen J. A power primer. *Psychological bulletin.* 1992; 112(1):155.
5. McDonald RP, Ho M-HR. Principles and practice in reporting structural equation analyses. *Psychological Methods.* 2002; 7(1):64-82.
6. Bloomsma A. Reporting analyses of covariance structures. *Structural Equation Modeling.* 2000;7(3):461-483.
7. Bartoff, J., Lai, T. L., & Shih, M.C. (2012). *Sequential experimentation in clinical trials: design and analysis* (Vol. 298). Springer Science & Business Media.