UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN
Version Date 3/30/2004
(Enter text in the **white space areas** below each numbered heading bar. **Expand the size of table cells as needed** – to multiple pages if needed.
See accompanying Instructions for explanation of headings and information to be provided)

1. PROJECT TITLE

"STAHR": Study To Assess Hepatitis C Risk among Young Adult Injection Drug Users in San Diego

2. PRINCIPAL INVESTIGATOR

Richard Garfein, PhD., MPH.

3. FACILITIES

This study is being conducted at:

- UCSD Antiviral Research Center (AVRC) located at 150 West Washington Street, San Diego, CA;
- San Diego Syringe Exchange Program Van located at 15th avenue between F street & G street and on 31st avenue, south of University avenue, San Diego, CA, which is operated by Family Health Centers of San Diego located at 823 Gateway Center Way, San Diego, California, USA 92102;
- San Diego County Health & Human Services Agency, Sexually Transmitted Diseases Clinic located at 3851 Rosecrans Street, San Diego, CA.
- Study staff and data management will be located at 3900 5th Avenue, Suite 200, San Diego, CA.

4. ESTIMATED DURATION OF THE STUDY

Two Years

5. SPECIFIC AIMS

The purpose of this study is to pilot test three methods of recruiting 18-30 year old IDUs in San Diego for a behavioral risk assessment interview and serologic testing for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection in order to determine the optimal method for ongoing national HCV surveillance. A total of 1000 IDUs will be recruited through 1) respondent driven sampling (RDS) (n=250), 2) street outreach (n=250), and 3) venue-based sampling using the syringe exchange program (n=250) and sexually-transmitted disease clinics (n=250).

The primary aims are:
1) To estimate the prevalence of HCV and HIV infection among IDUs recruited through each method.

2) To estimate the prevalence of and correlates of risk behaviors associated with HCV and HIV infection.

3) To identify differences in sociodemographics, risk behaviors, and HCV and HIV infection status between the three recruitment methods.

6. BACKGROUND AND SIGNIFICANCE

San Diego is the 2nd largest city in California and the 8th largest city in the U.S. with a population of 1.25 million and 2.9 million countywide. Among 6,742 drug and alcohol treatment admissions in San Diego County from 1/1/06 to 6/30/06, 1,456 (22%) participating individuals injected their main drug. Most of whom (72%) reported that heroin was the main drug that they used, 26% said methamphetamine, and 2% said cocaine/crack (Personal Communication – Robin Pollini, CEWG Representative). While injection drug use is a significant problem and injection drug users (IDUs) make up 18% of all AIDS cases in San Diego, little is known about the prevalence and incidence of hepatitis C virus (HCV) infection in this region. The only published study of HCV seroprevalence among IDUs in San Diego took place in a sexually transmitted disease (STD) clinic revealing that 43% of patients who reported injection drug use tested HCV antibody (anti-HCV) positive. In Tijuana, Mexico, which lies only 20 miles south of San Diego and shares the world's busiest land-border crossing, a recent survey found that 95% of IDUs were anti-HCV positive. San Diego's population is 52% non-Hispanic White, 30% Hispanic/Latino, 10% Asian, and 6% Black, providing a diverse region in which to pilot sampling methods for a national surveillance system. Furthermore, extensive drug use mapping in San

Diego followed by successfully recruiting over 500 IDUs using RDS for CDC's 2006,[1] National HIV Behavioral Surveillance (NHBS) IDU survey demonstrates feasibility for this study. The data will inform decision making by the CDC for a national HCV surveillance system and will also provide critically needed data on the prevalence and correlates of two important infections among IDUs in San Diego, HCV and HIV, which will inform health policy and future research.

7. PROGRESS REPORT/PRELIMINARY STUDIES

The current study has been funded and is nearing completion of the planning stages. This application is the first to be reviewed for protocol and consent form approval from the IRB. All subject recruitment, data collection, and data analysis will begin after IRB approval is received.

Dr. Garfein served as a CDC Epidemic Intelligence Service Officer in the Hepatitis Branch from 1997-1999, and then as a Project Officer in the Division of HIV/AIDS Prevention from 1999-2005, before joining the UCSD faculty in 2005. Dr. Garfein's seminal research on HCV prevalence and incidence among young adult IDUs in Baltimore, MD compelled CDC researchers to focus the CIDUS-II and CIDUS-III/DUIT[3] studies specifically on IDUs $\leq$30 years old. Dr. Garfein served as the CDC Project Officer on these two studies which enrolled and followed over 5,000 young adult IDUs. He currently conducts research among IDUs in Tijuana, Mexico using RDS and street outreach recruitment methods. Dr. Garfein will supervise the Study Coordinator, Data Manager, and Statistician and oversee all aspects of the study design, recruitment strategies, questionnaire development, IRB approval, data and specimen management, reporting to CDC, and analysis and dissemination of study findings in collaboration with CDC investigators.

Respondent driven sampling is an important component of this study; therefore, Dr. Garfein recruited Dr. Erik Volz to assist in RDS activities. Dr. Volz is a statistician who developed the RDS Analysis Tool software with Dr. Douglas Heckathorn, who first conceptualized RDS, at Cornell University. Dr. Volz began a post-doctoral fellowship at UCSD in September 2007, and will assist in developing methods to be used for implementing RDS in this study. He will also lead the analysis for at least one manuscript describing the results of RDS relative to other recruitment methods in this study.

Our team has experience collecting and managing biological and behavioral data with a high degree of accuracy and confidentiality. Shipping samples and data to CDC in a secure manner is critically important. Dr. Garfein has previously developed and employed such methods in the CIDUS III/DUIT study as well as a study of TB infection among vulnerable populations in Tijuana, Mexico. Community resources for IDUs have been identified and will be used in the proposed study to provide referrals for health care, drug treatment, and social services requested by the participants.

8. RESEARCH DESIGN AND METHODS

The study design is cross-sectional. Individuals age 18-30 years old, who report having injected drugs at least once in the past six months will be recruited to participate in a single assessment visit followed by a second visit to receive HCV and HIV test results. The assessment visit will include verbal consent to complete eligibility screening, informed consent, an audio computer-assisted self-interview (ACASI), pre-test counseling, and venipuncture for HCV and HIV testing. Participants will be asked to return in 2-3 weeks to learn their results and receive post-test counseling. Anti-HCV positive participants will be referred to **Family Health Centers of San Diego or County of San Diego Health Services** for medical services and care; HIV positive participants will be referred to UCSD Owen (HIV) Clinic or Family Health Center Ciaccio (HIV) Clinic. All participants will be offered referrals for drug treatment and other services.

STUDY PROCEDURES

Recruitment. Three methods will be employed to recruit a total of 1,000 IDUs; street outreach, RDS, and venue-based recruitment. For descriptions of these methods, refer below to recruitment section (#10 of the IRB application).

Screening. When potential participants come into the study site, they will receive information about the study aims and procedures and will be asked for verbal consent before beginning the screening interview (Appendix A). We will attempt to verify age by requesting photo ID; however, since our participants may not always have an ID, questions to assess age will be included in the screening instrument in different ways to reveal possible misrepresentation of age. At the end of the screening, eligible participants will be given the informed consent (Appendix B). The interviewer will first describe all information contained within the consent document and then ask the potential subject if s/he would like the interviewer to read the consent document to him/her or if s/he would rather read it him/herself. Interviewers will discuss the study and consent with the subject to determine understanding of the procedures and answer any questions the subjects might have. If they decide to participate in the study, they will sign the consent and will immediately begin the baseline assessment interview. However, if participants cannot complete the baseline assessment interview during that same visit, study staff will then schedule a baseline appointment for a later time. If the appointment is missed and it takes more than 30 days for the individual to return for the assessment, then the eligibility screener will be repeated to ensure that time-dependent criteria are still met. Participants who re-schedule for a baseline appointment will be reminded to bring a picture ID for verification of age, if they have it.

Participants who are not eligible for the study will be thanked for their interest, offered condoms and bleach kits, and informed that they are not eligible at the time. We will keep track of the number of participants screened and the eligibility data to assess potential selection bias in our study; however, no personally identifying information, such as names, will be retained on ineligible participants.

Pre-screening. All potential participants must be screened for eligibility at the study locations before taking part in the study. However, in some instances where it would be unreasonable to ask potential participants to travel long distances to the study location who might not be eligible, we will make the option of "pre-screening" available. Under these circumstances, study staff may choose to "pre-screen" potential participants in a private area before being referred to the study location for enrollment. A private area is defined as a safe location where no one else can hear or see the person's responses to the pre-screening questions (Appendix D), such as a park, sidewalk with few passersby, or secluded corner of a clinic waiting area. Additionally, study staff will ask potential participants for verbal consent before conducting the pre-screening and will be told that the questions are only part of pre-screening and will have to complete a full screening at the study site. During that time, outreach workers will tell potential participants if they are not eligible or that it looks like they may be eligible but must travel to the study site to be formally screened. Study staff will not record potential participants' names or other personal identifiers during pre-screening unless the individual agrees to receive a reminder call about the study. Individually identifying data will not be attached to the pre-screening data.

We request that written informed consent be altered and some elements be waived for pre-screening. The pre-screening will precede full written informed consent during the first face-to-face meeting with every participant including the decisional capacity assessment detailed in section 28 below. We request that informed consent be altered for the screening given the following criteria stated in 45 CFR 46.116(d):

1. The research [i.e., pre-screening] involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation [i.e., being screened].

We request waiving documentation of informed consent for pre-screening only, which may be obtained if "the research presents no more harm than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context" [45 CFR 46.117I(2)]. Following is justification for these requests.

Pre-screening will only be used for the street outreach phase of the study detailed in section 10 below. Outreach workers will be able to provide information and directions to the study site. Outreach workers will also have the option of pre-screening participants in a safe location if a potential participant might be hesitant to travel to the study offices if they are not eligible. Additionally, participants will be asked for verbal consent before beginning pre-screening and will be reminded that they will need to re-screen at the study offices and no information gathered during pre-screening will be recorded, unless they request a reminder call. The screener takes less than 10 minutes to complete, and the participant may refuse to participate in the study immediately after pre-screening; agreeing to take part does not preclude

individuals from terminating participation at any point during the pre-screener or the study.

Pre-screening is not easily completed if staff must cover all required criteria of informed consent prior to pre-screening. Such a consent process requires much more time than screening itself, and potential respondents could grow weary and discontinue the conversation. In addition, a signed consent for the pre-screening would increase the risk of confidentiality loss for individuals who do not enroll in the study, because it will create the only identifier linking these individuals to their screening information. After pre-screening is completed, individuals who appear to be eligible will be told that they will need to go to the study offices to get officially screened (Detailed description of pre-screening procedures see Appendix D). Outreach workers will answer any study related questions.

Baseline Visit. After being recruited and screened for eligibility, participants will typically continue directly into the baseline visit procedures the same day as the screening. If the baseline procedures cannot be started because there would not be sufficient time to complete the entire visit, the participant will be given an appointment to return at a later date for the baseline visit. Baseline visit procedures include:
1) Review and sign the consent form;
2) Complete a behavioral assessment using ACASI technology;
3) De-brief after the ACASI assessment to address participant questions or concerns;
4) Receive HCV/HIV pre-test counseling and have blood drawn;
5) Provide locating information; and
6) Receive compensation for time and scheduled to receive test results and post-test counseling 2-3 weeks later.

Informed Consent Process. Study staff will describe the procedures, risks and benefits of participation (e.g., the fact that the study participants may feel uneasy about sharing personal experiences and answering questions about drug use and sex). Moreover, participants will be informed about the nature of confidentiality. Prior to participation in the baseline counseling and testing procedures, the participant will read (or ask a staff member read aloud to them) and sign a consent form detailing the study procedures, risks, benefits and nature of confidentiality (Appendix B – Informed Consent Form). Participants will be informed that all links between the participant's study data and identifying information will be broken and hard copies of the locator information will be destroyed within six months of the end of the study. The staff member obtaining consent will also sign the form. Each participant will also receive an unsigned copy of the consent form and "The Experimental Subject's Bill of Rights" to keep for their records. Staff will answer questions about the study and consent form or any other issues that may arise during the process.

Behavioral Assessment. The behavioral assessment will be administered through ACASI (Appendix C provides a paper version of the assessment). The attached paper version is now being tested by the investigators for compatibility with the ACASI technology, and a final version will be provided to the IRB before beginning data collection.

The ACASI system displays each assessment question on a computer monitor while simultaneously playing an audio recording of the question through headphones to overcome problems of illiteracy. Participants enter their responses to the assessment questions directly on the computer. After consent and a brief rapport building discussion to put the participant at ease, staff members who have been trained in the use of ACASI will initiate the interview by entering the participant's unique ID number into the ACASI program. Staff will demonstrate the ACASI system to each participant and answer any questions about its use. There is a practice module that presents every type of response option used on the survey. This practice allows the participant to get used to using the computer. Participants will then complete the baseline assessment, which should take approximately 55 minutes. During this time, the staff member will remain close by (but in a position where participant's responses cannot be seen) to answer any additional questions or address any problems. Baseline assessment data will be immediately stored on the computer in which the data were entered and will be identified with only the participant's study identification number (no names). Once the interview ends, the participant's data file will be closed and can only be reopened by the study's data manager. The proprietary software that we are using for ACASI (QDS, Nova Research Inc.) is distributed in separate modules for developing, running, and compiling data from ACASI interviews. The only module that will be installed on the interview computers is the one for running the interview, making the interview data files virtually unintelligible. ACASI interview files must be transferred to the data manager's computer, which will be equipped with the Warehouse Manager module necessary for managing and interpreting the interview data. All data entry computers will be password protected to prevent access by non-staff members and ACASI data will be stored so that data will not be accessible until it is removed from the

interview computer and place on a data management/ analysis computer.

The ACASI software provides the ability to program checks that can detect inconsistencies in the participant's responses. These checks may be used to point out the inconsistency and invite the participant to adjust their response if they made a data-entry error. An additional check will be used to reassess the participant's self-reported injection drug use. Since injecting drugs during the past 6 months is an eligibility criterion, which will be asked during the screening process, the participant will be expected to answer questions related to injection drug use in the past 6 months on the assessment. If they indicate that they had not injected during the past 6 months on the ACASI interview, they will be given one opportunity to re-answer the question in case a data entry error occurred. If their response remains unchanged, then a screen will pop up instructing the participant to call the staff member. The staff member will probe further with the participant to determine their injection status. As these probes are intended solely for the purpose of getting non-injectors to admit to not injecting drugs, participants will be assumed to be providing valid responses until they admit otherwise. Thus, to avoid introducing bias, participants who maintain that they do inject drugs after being asked the probes will NOT be made ineligible even if the staff member is in doubt. If an individual is discovered to be ineligible, all data collection procedures will cease. Staff members will then follow procedures for terminating a participant from the study in a manner that is decisive yet considerate to the individual and does not compromise the reputation of or future recruitment effort for the study. Ineligible individuals will still be offered prevention materials and referrals for HIV testing and other services.

Post-Interview Debrief. The behavioral assessment asks participants difficult questions about previous experiences of childhood physical and sexual abuse, substance use, and sexual risk behaviors that may cause some participants to feel upset. Study staff, including counselors, will not have access to the computerized behavioral data. In order to immediately and proactively protect and provide appropriate help and referrals to participants, study staff will provide participants an opportunity to de-brief about the interview and will be provided with appropriate referrals. All participants will be informed at the beginning of the de-briefing that the counselor is required by law to report child abuse to the appropriate authorities.

Services. At follow-up, anti-HCV positive participants will be referred to the Family Health Centers of San Diego or **County of San Diego Health Services** for medical services and care; those who are HIV infected will be referred to the UCSD Owen (HIV) Clinic or Family Health Center Ciaccio (HIV) Clinic. **Participants who request written documentation of their positive test result will be provided with a letter of referral for their medical provider. The letter can be used by participants seeking medical care for their positive study test results and highlights that the results are for research purposes only and not intended for patient diagnosis or patient management (Appendix I and J).** All participants will be offered referrals for drug treatment and other services. Counseling and educational materials (Appendix H) will resemble those in CIDUS III/DUIT.[3] Identification, establishment and maintenance of rapport with agencies offering relevant services for the study participants will be ongoing throughout the data collection phase of the study. Counseling and referral services will be made available to study participants throughout the end of the recruitment phase, or until all participants have received their test results.

HCV/HIV Pre-test Counseling and Blood Draw. Before venipuncture, participants will receive combined HCV and HIV pre-test counseling. For purposes of quality assurance and counselor evaluation, some counseling sessions will be observed by site supervisors and investigators. The consent form (Appendix B) indicates that some counseling sessions may be observed. We expect that up to 5% of all sessions will be observed. After completing informed consent, baseline assessment, and combined HCV/HIV pre-test counseling, participants will provide a blood specimen by venipuncture. Trained phlebotomists, experienced in obtaining blood from IDUs who frequently have scarred veins, will perform venipuncture according to standard clinical practice. **A total of 20mL (about 1.5 tablespoons) of whole blood will be collected.**

Mechanism for Hepatitis A and Hepatitis B Vaccination. Hepatitis A/B vaccination is recommended for HCV infected individuals and is available to adults at high-risk for HCV through clinics and agencies throughout San Diego with eligibility linked to patient risk factors. Study participants will be referred to these clinics to receive these vaccines. Given HIPPA and other patient confidentiality protections, significant barriers exist to obtaining vaccination records directly from these clinics. Thus, participants will be given $5 compensation for time and travel in the form of cash, scrip, or gift cards to return after each dose (up to 3) and show documentation that the vaccine was received. We have

experience doing this in another study (CIDUS III/DUIT)[4]. These data will be recorded using the participant's study ID number so that it may be merged with behavioral and laboratory results data for analysis. Data collection on vaccine uptake will be conducted until approximately 60 days after the last participant interview in order to allow time to compile and report these data to the CDC. The vaccinations are not part of the study and the study will not be paying for it. We will only refer participants to places where they can receive free vaccines. Payment is only give to participants for time and travel to show us their vaccination card after they receive the vaccine.

In most cases, we will refer participants to one of Family Health Centers (FHC) service sites (Downtown, Beach Area, North Park, El Cajon Blvd/La Mesa). The most feasible option is to refer participants to the FHC North Park facility's Tuesday Night Clinic. The Tuesday Night Clinic principally exists for MSM and transgender individuals, but also sees a number of IDUs. The registration and eligibility process is streamlined at this facility and participants can also receive STI screening if needed. The fee ($20 for vaccine series) can be waived in for clients who are unable to pay, which will always be the case for our study participants. The North Park facility is located on a principal bus transit hub and is one of the largest non-urgent care health providers for the uninsured in the area.

Locator Information. During their baseline visit, participants will be asked for their locating information (Appendix F). It will be explained that this information will be used to try to contact participants who fail to return for the result visit and actively locate participants with positive results. We are also cognizant of the fact that some participants may be homeless or have unstable housing and may not be able to provide a fixed address. Information that is collected will be entered into the Participation Database (discussed in Data Management below) and then the paper copy will be kept in a locked file cabinet until 6 months after the end of the study at which time it will be destroyed .

Tracking Participation & Avoiding Duplicate Enrollment. Since we will use three different methods of recruitment for this study, but eligibility criteria indicate that a participant can only enroll once, we will use a number of methods to assist our staff and potential participants from mistakenly participating in duplicate enrollment. First, we will keep a comprehensive database "Participation Database" that will aid in tracking participants' personal information, contact information, scheduled and completed appointments (including appointment times and dates). This database will not contain the participant's ID number, which will remain separate from the Participation Database to protect participant confidentiality. The "Locator Information form" (Appendix E) for study participants will also include names and contact information of friends, family, and acquaintances whom we may contact or leave messages with should we be unable to find participants to give them their HCV and HIV test results. No information about the participant, the study, or the participant's HCV/HIV test results will be disclosed to these contacts. Messages will only indicate the name of a staff member, and that we would like the participant to come to a follow-up visit and leave a phone number to call back. Staff will make at least 3 attempts to contact each participant who have not returned for their test results. Special effort will be devoted to contacting participants whose test results are positive for early or acute infection. Second, a single study logo will be used throughout all methods of recruitment so that potential subjects can easily identify the study and study staff. For outreach and venue based recruitment, study staff will wear t-shirts with the study's logo. All printed material will be identified with the same memorable logo. When participants complete the baseline interview, we will give them a small gift, such as a key chain or a condom pouch imprinted with the study's logo. We anticipate that the logo will aid participant's recollection about previous participation should they complete the screener a second time. Last, we will take biometric measures of participants forearm length and wrist circumference. This will serve as an additional check to help us identify participants who attempt to reenroll without our knowledge.

Results Visit. Participants will be given appointments to return 2-3 weeks after the assessment visit to **receive HCV and HIV antibody test,** nucleic acid test (NAT), and enzyme immunoassay (EIA) test results and post-test counseling. Some post-test counseling sessions may be observed by site supervisors or investigators for purposes of quality assurance and counselor evaluation as indicated in the consent forms. We expect that up to 5% of all sessions will be observed. A combination of reminder letters, phone calls, emails, text messaging and home visits will be employed to minimize the number of participants who fail to receive their test results. Participants who are anti-HCV positive will be referred to **Family Health Centers of San Diego or County of San Diego Health Services** for medical services and care; those who are HIV infected will be referred to the UCSD Owen (HIV) Clinic or Family Health Center Ciaccio (HIV) Clinic. All participants will be offered referrals for drug treatment and other services as desired by the participant. Every participant will also have the option of not getting their test results if they don't wish to receive them.

Reimbursement. At the end of the baseline assessment, participants will be reimbursed $25 for their time and travel costs and scheduled for an appointment to receive their test results and post-test counseling. Participants will be given a small reminder card that specifies the date, time, and location of this appointment. At the end of their result visit, participants will be reimbursed $10 for their time and travel costs. For participants who get their Hepatitis A or B vaccinations, they will receive a $5 reimbursement when they bring documentation showing that they received each vaccination (up to 3 shots). Participants, who are in the RDS recruitment wave and are given coupons, will be reimbursed an additional $10 for each person they refer who is eligible to take part in the study. All reimbursements provided to participants will be in the form of cash, script or gift cards.

SPECIMEN COLLECTION, HANDLING AND STORAGE.

Serologic Samples. **All serologic samples will be labeled with the participant's study ID number and date of blood draw. Names will never be placed on any samples**. Following pretest counseling, participants will have **three** vacutainer tubes (one EDTA, one SST, **and one PPT**) of blood drawn via venipuncture by a trained phlebotomist. The tubes will be spun and one 1mL aliquot from each tube will be placed in cryovials (2 total) before freezing at -70 C for HCV nucleic acid testing at the CDC. One aliquot (1.5 mL) of serum will be sent for HCV antibody testing at the San Diego County Department of Health Services (SDCDHS) Lab. **The PPT tube** (5.0 mL) will be sent **processed at** the AVRC lab and **sent** for HCV and HIV **Nucleic Acid Testing (NAT)** at the American Red Cross lab. **HIV antibody-positive samples will be sent to** Blood Systems Research Institute**, San Francisco, CA for Sensitive/Less-Sensitive Enzyme-Linked Immunoassay (S/LS-EIA) testing to differentiate acute from chronic HIV infection.** All remaining serum and plasma in the vacutainer tubes will be placed in cryovials, frozen, and sent to the CDC for repository. All cryovials will be labeled with only the participant's unique ID number and date of blood draw. Cryovials will be placed into cryovial boxes and a paper log matching the box will be completed to facilitate future sample retrieval. **Once each month** the cryovial boxes and specimen logs will be shipped to the CDC per CDC instructions for supplemental testing and repository. Samples will be stored for up to 50 years and may be used to test for HIV, HCV, and other infections spread by sex or injection drug use. Genetic testing may be performed to detect infection by human pathogens, but will not be used on the participant's DNA.

HIV and Hepatitis C Virus Screening. HCV antibody screening will be performed at the SDCDHS Lab using the Abbott Axsym microparticle EIA system. Using CDC published guidelines[2], specimens that test repeatedly reactive with a s/co ratio $\geq$10.0 will be considered anti-HCV positive. Repeatedly reactive specimens with s/co ratios <10.0 will have supplemental testing using RIBA at Quest Laboratories, Santa Monica, CA. All samples will be submitted and tested by the San Diego County Public Health Laboratory using only participant ID numbers. The Data Manager will receive results by study ID instead of names and merge the results with participant interview data for analyses.

In our effort to provide participants with a more accurate and up-to-date diagnosis, we will give each participant the option of **NAT and S/LS-EIA** testing as well as HCV and HIV antibody testing. NAT testing captures HIV-1 and HCV RNA in blood samples. This test will allow the simultaneous detection of all known HIV-1 and HCV subtypes with sensitivities designed to reduce the window period of false negative results from standard HIV antibody testing (EIA), while maintaining the ability to discriminate positive from negative specimens, even at very low copy numbers[5]. This method is currently used universally to screen blood donations for transfusion in the United States. The samples will be analyzed daily by the American Red Cross (ARC) in St. Louis, Missouri. NAT detection of HIV-1 and HCV infection will be performed using mini-pools of 16 samples. The S/LS-EIA testing strategy has been widely applied in research settings for discriminating early HIV infection from chronic HIV infection and for detecting recent seroconverters, thereby providing better estimates of HIV incidence rates. S/LS-EIA testing will be performed at the Blood Systems Research Institute located in San Francisco, CA.

Serologic specimens will be labeled with the participants' study ID numbers instead of their names to protect their confidentiality. The laboratories and CDC will never receive the participants' names or any other personal identifiers.

Availability of HCV and HIV Results for Participants. Participants will be asked to return for HCV and HIV test results, posttest counseling, and referrals for clinical care if positive. Prior experience with this population revealed that

while test results are desired by study participants, they frequently miss the originally scheduled results visit. Therefore, we will continue to make test results available for at least 2 months after the last participant is interviewed.

Monthly Anti-HCV Results Reported to the CDC. On the 15th day of each month, an electronic file containing HCV and HIV antibody and NAT test and LS HIV test results will be sent to CDC Project Officer. Results will only be identified by the participants' study ID to maintain confidentiality and allow CDC to anonymously link results to interview data. The final data file will be sent to CDC within 60 days of completing all interviews.

DATA MANAGEMENT

All staff members have completed UCSD research ethics training, and all have current UCSD IRB training certificates. In addition, they will receive training in human subjects protection, voluntary informed consent, and research ethics. Utmost care will be taken when contacting participants about enrollment, participation and follow-up reminders. Study staff will only talk to the participant directly unless the participant has authorized staff to leave a message or have contact with others pursuant to follow-up visits. Staff will never disclose information about the participants or the study to anyone, not even those individuals that participants have given staff to speak with about locating participant or leaving a message for a participant.

Locator Information. Obtaining reliable locator data at the baseline visit is necessary to contact participants who do not return for their results visit and for notifying participants with early or acute infection prior to their appointed results visit. Therefore, all participants will be asked to fill out a locator form which will include: name, address, phone number and e-mail address to contact the subject for the next study visit. We will also request the name, address, and phone number of three relatives, friends or others who are likely to know how to contact them when the next study visit is due. Their relationship to the subject will be noted. Contact information will specify whether or not study mail can be sent to this address, and whether or not staff members have permission to leave a message, mention the name of the study, and/or ask individuals where we might find the participant. The language used to communicate (English or Spanish) will also be noted. Participants will also be asked to suggest the best way to contact them (for example, what time of day it is best to call them and which number to try first). The locator form asks other ways to reach the subject, including: park, café, bar, corner or needle exchange where they spend time; if it is okay to come by their residence and/or leave a message; and whether the participant has other ideas how they could be contacted if other information fails.

There will be one paper log and one electronic file listing names and corresponding IDs of enrolled participants (Linking File). The paper log will be kept separate from all other study-related data in a locked file cabinet in the office of the project coordinator and will only be accessible to staff who need that information (e.g., staff who are about to start the baseline assessment on the computer for a participant or the counselor who must link the participant to his/her test results). The electronic file will be a password protected computer file in the project coordinators office.

Baseline Visit. The baseline ACASI assessment begins with the staff member entering a unique participant ID code into the computer program. This ID number will be used to link the participant's interview, laboratory, and participation data for analysis purposes. One advantage of the ACASI system is that there are no paper copies of the data. Safety and back-up of computer copies of the data are discussed below. Each biologic specimen sent for testing will be labeled with study name, participant ID and date of collection.

At the end of the baseline visit, 4 records will exist for each participant:
1) Name Only: Locator Information & Participation Database with name and locator information.
2) Name and IDs: Paper log stored in locked file cabinet and an electronic password protected computer file in the Project Coordinators office with need-based access only.
3) ID Only: Eligibility screener and baseline assessment data stored on password protected computers and a password protected computer server.
4) ID Only: Blood samples sent for laboratory testing and blood stored for future testing (if consent to store blood is granted). This record will also include test results.

For each individual participant, the Locator Information & Participation Database will include the following elements: study ID; date enrolled; form of enrollment strategy (RDS, venue-based, street outreach); # attempts to contact; date completed assessment; missed visit (Y/N); reason; post-test counseling session completed (Y/N); Hepatitis A/B vaccine records, and withdrawal from the study (administratively or participant request). This database will be password protected and accessible only to project staff who need tracking information, such as the data manager and recruiters. At the baseline visit, participants will fill out a Locator Information form. This form will be entered into the "Participation Database" and the paper copy will be kept in a locked file cabinet in the project coordinators computer separate from all laboratory results and assessment data until 6 months after the end of the study, at which time the Locator Information will be destroyed. As the study continues to accrue participants, this will allow study staff to screen out people who have already participated in the study.

Behavioral Data Storage. Because behavioral data are being collected by an ACASI system, data will be automatically stored on the interview computer, and there will be no paper copies of data. Each laptop computer used for computer assisted interviewing will be password protected and cable locked to a piece of furniture in the interview space. An additional password will be needed to access the ACASI program containing the assessment data. Because a separate "Warehouse" module is needed to read a data file after the interview is complete, this software will not be loaded on the interviewing computers to further protect the confidentiality of the data. Each day throughout the data collection process, completed ACASI interviews will be backed up as password-protected files to a secure, password protected UCSD computer network server with access limited to only the study's PI, project coordinator, and data manager. Each week the interview files will be transferred from the password protected computer network server to the Data Manager's computer before being deleted from the interviewing computers. If the network server is down, the project coordinator will use a USB drive that provides encryption and data recovery to transfer the files from the interview computers to the data manager's computer. Screening and assessment data with ID numbers only (no names) will be sent to the CDC central data manager on a monthly basis as encrypted files by e-mail or Secure Data Network (SDN). Access will be restricted to data during the course of the study. After the study, when contact information has been destroyed for all participants, staff will be able to access the data for data analysis. The fact that data will be stored in this manner will make it extremely difficult for a person's data to be linked with their name.

Biological Samples and Data Storage. Management of laboratory testing data will be conducted in such a way as to provide results to participants on-time and allow frequent interim data analysis for quality control purposes. HCV and HIV test results will be compiled locally and sent to the CDC monthly in the form of an encrypted line listing or data file containing participant ID number, specimen ID number, visit date, test date, and HCV and HIV test results. The data will be sent each month in electronic format either via mail or SDN. The CDC will perform periodic analyses for quality control.

9. HUMAN SUBJECTS

ELIGIBILITY CRITERIA. To be included in the study, the participant must:

1) be 18-30 years old;
2) self-report injection drug use in the last 6 months;
3) be a current resident of San Diego County;
4) agree to blood draw for HCV and HIV testing;
5) provide contact information;
6) not be enrolled in other waves of the study.

Over a 15 month period, up to 1,000 young IDUs will complete pre- and post-test screening and the baseline questionnaire. We anticipate that at least 30% of participants will be female, with a goal of having 50% male and 50% female. Additionally, we expect significant ethnic diversity due to the diversity of the populations of young IDUs living in San Diego.

10. RECRUITMENT

Three methods will be employed to recruit a total of 1,000 IDUs between the ages of 18 and 30 years. The methods are as follows:

Respondent driven sampling (RDS): At least 250 participants will be recruited using RDS, a chain referral sampling approach that uses mathematical modeling to produce prevalence estimates that are unbiased by selecting initial participants or "seeds" in a non-random way.[1] Briefly, a diverse group of seeds (heterogeneous in age, gender, drug of choice, and recruitment venue) will be selected to initiate the process. Seeds will be current IDUs who project staff members identify as having large social networks and are popular among their peers. Although individuals tend to recruit participants similar to themselves, studies of RDS show that equilibrium is reached within approximately 4 to 5 waves of recruitment eliminating bias introduced by non-random seed selection.[1] After providing informed consent, seeds undergo the study procedures described previously and are then asked to refer their peers using three uniquely coded coupons containing the study name, interview locations, and a brief explanation of the study. For each new participant who is recruited by bringing back a coupon, the seed will receive $10. Recruitment waves continue as those recruited by coupons are given 3 coupons to recruit members of their own social network. Exclusion of individuals who have participated in the study through other recruitment methods could disrupt the natural propagation of RDS recruitment chains; therefore, RDS recruitment will be completed before initiating the other recruitment methods.

We will keep a "Coupon Tracking Log" to record the following: 1) each coupon's number, 2) the date a coupon was given to a participant for distribution, 3) the study ID number of the participant to whom the coupon was given for distribution, 4) the date each coupon was returned, 5) whether the person returning a coupon meet the study enrollment criteria of current injection and age between 18-30 years old and, if that person enrolls in the study, 6) the new participant's study number, 7) whether compensation was provided to the participant who distributed the coupon, 8) biometric measures, and 9) personal identifiers such as gender and tattoos. The coupon tracking log will not include participants names and will be maintained on a password protected laptop computer in a separately password protected file. This computer will not contain any of the interview or test results data.

Venue based recruiting: At least 250 participants each will be recruited from two different venues that are accessed by IDUs. The syringe exchange program (SEP) run by Family Health Services of San Diego and sexually transmitted disease (STD) clinics operated by the San Diego County Department of Health Services (SDCDHS). Between July 2006 and June 2007, the SEP enrolled 442 new IDUs in the Downtown and North Park areas of San Diego with 3,628 client visits during that time. During 2000-2006, the main county STD clinic on Rosecrans Street averaged 445 IDU clients per year; 145/year were <30 years old. Overall, 31% of IDUs were anti-HCV positive, of which 12% of those were <30 years old. Thus, a second STD clinic in the North Park neighborhood that serves a population with a high prevalence of drug use will be included. If necessary to meet our recruitment goals, recruitment may also take place at other STD clinics operated by Family Health Services of San Diego.

Street outreach: At least 250 plus participants will be recruited by having outreach workers pass out recruitment cards, leaving posters and leaflets at recruitment locations, and encouraging current study participants to inform their peers about the study. Outreach workers will approach individuals in neighborhoods, streets, bars, and other "hang-outs" where young IDUs are known to frequent. During these encounters, the outreach worker will attempt to engage individuals in conversation by offering HCV/HIV prevention materials (i.e., bleach kits, condoms and personal lubricant, and educational pamphlets). During these encounters, the outreach worker will also hand out recruitment cards (Appendix G) with information about the study. In order to avoid requiring disclosure of the individuals' injection status, they will be told that they can take the card for themselves or someone they know who might be interested in the study.

Outreach workers will receive extensive training in how to approach and engage potential participants in these community settings. Ethical guidelines regarding professional conduct will be enforced for all outreach workers. Outreach workers will work in pairs to ensure their safety and adherence to the study protocol. Outreach workers will be able to provide information and directions to the study site or pre-screening when appropriate (see pre-screening above).

Recruitment sites are located in well-known areas of high drug traffic or drug use or where young injectors are known to congregate. Possible recruitment locations have been previously identified and mapped through ethnographic methods or through community contacts, key informants and a Community Advisory Board (CAB). In addition to recruiting

participants directly from these recruitment areas, some participants may be indirectly referred to the study by friends who have participated in the study or who heard about the study but were ineligible. In these cases, participants will not identify their friends to study staff but will tell their friends about the study and encourage them to be screened for eligibility (respondent driven sampling – described above). When necessary, permission to recruit around business establishments will be secured prior to initiating recruitment.

Individuals who are willing to be contacted by the project staff to be reminded to come to the study site for eligibility screening will be asked for their name, telephone numbers where they can be reached, and whether a message may be left. All contact information obtained during such outreach encounters will be destroyed once potential participants have been found to be ineligible, participated in the study and completed both visits or they have indicated their desire not to participate. Individuals who are not asked contact information, or who do not wish to provide this information, will be given a number to contact the project staff. A pre-screening script and a screening script are provided in Appendix D and Appendix E.

11. INFORMED CONSENT (Note: provide information in Section 28 on Surrogate Consent and Decisional Capacity Assessment, if applicable)

Prior to undergoing the baseline assessment protocol, the participant will read and sign a consent form detailing the study procedures, risks, benefits and nature of confidentiality (Appendix A – Consent form). The study procedures will be explained to the participant and s/he will be informed that all links between the participant's study data and identifying information will be broken and hard copies of the locator information will be destroyed within six months of the end of the study. The study staff obtaining consent will also sign the consent form. Each participant will also receive an unsigned copy of the consent form to keep for their records. Staff will be available to answer questions about the consent forms or any other questions that may arise during the process.

Taking part in any of the study activities (baseline assessment and blood draw) involves minimal risk to participants. The informed consent procedures will make clear all of the potential risks of study participation. There are minimal risks associated with the blood draw and counseling sessions. The only medical risks in the study would be from drawing blood. There may be discomfort or bruising associated with venipuncture. All personnel involved in blood drawing in the study will be experienced phlebotomists and trained to minimize discomfort and ease the blood draw process. Trained HIV counselors will conduct HIV/HCV pre- and post-test counseling one-on-one with participants in a private setting. The counselors will be trained to recognize and appropriately refer for care any participant that is at risk for hurting his/herself or others.

In all cases, fully informed consent will be obtained. Any participant who is deemed to be incapable of making a fully informed decision about participation due to the influence of alcohol or other intoxicating substances will be rescheduled for an interview at a later date. Dr. Garfein will be available on-site or by telephone to answer any questions raised by a participant. A copy of the consent form, which includes a description of the study, will be provided to all participants. Participants will also be giving a copy of "The Experimental Subject's Bill of Rights." All participants will sign the informed consent before participating in any research activities.

12. THERAPEUTIC ALTERNATIVES (therapeutic studies only)

N/A

13. POTENTIAL RISKS

Confidentiality. There is a risk to the privacy of participants because they will be asked about private topics, such as drug use and sexual behaviors. However, all behavioral data will be collected via ACASI and stored with only participant's ID numbers. The researchers will keep the information that is provided by the participants as confidential as possible, but complete privacy cannot be absolutely guaranteed. Additionally, participants will have the option to skip any or all questions they do not want to answer. Furthermore, all data will be stored in encrypted files on password protected computers using study identification numbers instead of names and will be accessible only to the study investigators, in order to protect participants' confidentiality.

The investigators possess extensive experience protecting research participants' confidentiality through numerous studies involving thousands of participants. Through the use of unique ID numbers, password protected data files,

locking filing cabinets, and extensive staff training, prior breaches of confidentiality have not occurred. Identical methods will be employed in the current study to minimize the risk of a breach of participants' confidentiality. Although the risk will be minimal, participants will be informed about the possibility of this occurring and what the potential impact could be during the informed consent process.

Other Questionnaire Related Concerns. In this study participants will be asked personal questions about drug use, sexual activity, and history of traumatic events, such as child abuse and non-consensual sex. Some participants may find these questions embarrassing or even upsetting. In order to reduce embarrassment, participants will complete their questionnaires in privacy and will be allowed to decline to answer any questions that they feel too uncomfortable responding to. Additionally, study staff will de-brief participants about the questionnaire to identify those who may have become upset by questions that they encounter. For upset individuals requiring immediate attention a psychologist will be available. Additionally, participants will be referred to further counseling if they are upset by a past event in their life.

Blood Draw and Test Results. Drawing blood may cause discomfort and bruising. All personnel involved in blood drawing in the study will be experienced phlebotomists and trained to minimize discomfort and ease the blood draw process. Some participants may be confused by their HCV and HIV results. To minimize this possibility, staff will; 1) provide standard messages based on the results; 2) encourage care seeking and talking with medical providers about health care issues; 3) seek immediate supervision and assistance, if necessary, to handle emotional upset; and 4) seek assistance and supervision from the medical consultant on the study if necessary.

14. RISK MANAGEMENT PROCEDURES

Risks to privacy will be minimized through staff ethics training, layered data security and by restricting access of sensitive information to staff members who have a specific need for the information.

1) Training: All study staff will be trained in the ethical treatment of study subjects and subject data with special emphasis on maintaining confidentiality.
2) Data Security: All subjects will be assigned an identification number at the screening interview which will be used in place of names on the baseline assessment, biological samples and test results. All participants' information and test results will be entered directly onto a password protected project computer. All data files will be encrypted and password protected with passwords known only to the Principle Investigator and Study Coordinator. All test results stored at partner medical facilities will be secured according to those facilities' data security protocols only with ID identifiers. Test results will be passed between medical facilities and Study Coordinator in computer files protected with layered encryption. No names will be used in this process, only study IDs.
3) Restricted Access: Laptop computers will all be secured with password access and available only to study staff members. Laptops will be locked in cabinets in the secured study office when not in use.

The only identifying information on participants will be on the consent form and the locator form, which will assist us in locating participants 2-3 weeks later for test results if they do not return as scheduled. These forms will be kept in a locked filing cabinet in the study coordinator's office and will be separate from all other study-related data.

Risks to embarrassment and/or emotional upset will be managed through ensuring privacy for the participant while s/he completes the questionnaire; enabling the participant to decline to answer questions for which s/he is too uncomfortable to answer; and providing de-briefing and psychological care and referral when necessary.

15. POTENTIAL BENEFITS

Few direct benefits to participants are anticipated. Participants will receive free HCV and HIV tests and will be referred to a local hospital and other local groups for health services and support if found to be infected with HCV or HIV. Referrals for free hepatitis vaccination and for mental health, counseling and other supportive services will be provided, along with printed information about the prevention of HCV, HIV and sexually transmitted diseases, to all participants. Participants will also be offered free bleach kits and condoms.

While behavioral data collected as part of this study may have few direct benefits to participants, the information gathered on HCV and HIV prevalence will be the most comprehensive ever obtained about young adult IDUs in San Diego enabling opportunities to assist the community as a whole. These data will be used for future public health planning in the region. Specifically, information learned from this study will help determine the prevalence of HCV infection in this previously unstudied population, and identify risk behaviors that should be targeted for interventions. In addition, the methodologies developed for this study will form the model on which the CDC will base a national HCV surveillance system.

16. RISK/BENEFIT RATIO

Given that the potential risks to the participants are relatively minor, and that there is the potential benefit to improve HCV and HIV prevention services for young IDUs in San Diego, we feel that the benefits outweigh the risks. To our knowledge, this is the first study of HCV and HIV infection among young adult IDUs in San Diego.

17. EXPENSE TO SUBJECT

None other than time taken to participate and travel to the study site.

18. PAYMENT FOR PARTICIPATION

Participants will be reimbursed $25 for their time and expenses to attend the assessment visit, complete the assessment and have their blood drawn. Participants will be reimbursed $10 to return for their result visit and $5 for returning to the study with their vaccination record after receiving HA/HB immunization. Participants in the RDS phase of the study will receive $10 for each new participant (maximum 3) who is recruited into the study by providing study staff with an RDS recruitment coupon. All reimbursement provided to participants will be in the form of cash, scrip, or gift cards.

These amounts are meant to reduce barriers to participation, without being coercive, by compensating participants for basic expenses (e.g., time away from earning income and transportation to the study site).

19. PRIVILEGES/CERTIFICATIONS AND LICENSES

Richard S. Garfein, PhD, MPH (Principal Investigator). Dr. Garfein is an Associate Professor in the Division of International Health and Cross Cultural Medicine in the Department of Family and Preventive Medicine at UCSD. He was trained as an infectious disease epidemiologist at Johns Hopkins University, School of Hygiene and Public Health where he earned his PhD studying HCV infection among young adult IDUs, and San Diego State University, School of Public Health where he earned his MPH degree. Dr. Garfein worked for nearly 8 years at the Centers for Disease Control and Prevention as an epidemiologist, first in the Division of Viral Hepatitis and later in the Division of HIV/AIDS Prevention where he lead several studies of bloodborne viral infections among IDUs. Dr. Garfein will be responsible for overseeing all aspects of the study and will take a lead role in writing manuscripts from the study.

Lydia Drumright, PhD (Post Graduate Researcher). Dr. Drumright has extensively studied non-injection drug use and sexual behaviors as risk factors for HIV transmission and acquisition in San Diego. More recently she has examined factors associated with the force of HCV infection among IDUs in Tijuana, Mexico. In the current study she will assist in survey instrument design, participant recruitment, interviewing, data management, and contribute to publication and presentation of study findings.

Erik Volz, PhD (Statistician). Erik Volz is a post-doctoral fellow (NIH T32) at the Antiviral Research Center of the University of California- San Diego. Dr. Volz specializes is survey methodology targeting hidden populations such as drug injectors and MSM and has several years experience developing methods and statistical techniques for Respondent Driven Sampling. Dr. Volz also has extensive experience in mathematical epidemiology and the modeling of infectious diseases, especially STI's in contact networks. Dr. Volz will be responsible for managing RDS coupon distribution and redemption, RDS implementation, data analysis, and significant contributions to manuscripts and presentations from this study.

Jazmine Cuevas, MPH (Study Coordinator). Ms. Cuevas is an SRA III in the Division of International Health and

Cross Cultural Medicine in the Department of Family and Preventive Medicine at UCSD. Her primary responsibilities will include the supervision and training of study staff, planning and assigning work tasks, managing all aspects of data collection, quality control and assurance, preparing and maintaining human subjects' protocols, and making original contributions to presentations and publications.

Eyasu Teshale, MD (Collaborator). Dr. Teshale is an epidemiologist in the Division of Viral Hepatitis at the Centers for Disease Control and Prevention and is the Project Officer for the contract that is funding this study. Dr. Teshale will provide consultation on the study design and implementation. He will also be involved in interpreting the results of data analyses and making original contributions to manuscripts written from this study.

Davey Smith, MD (Collaborator). Dr. Davey Smith is a clinical researcher at UCSD. Since April 2004 he has been involved in the UCSD AVRC's Early Intervention and Bridge Programs services. The Early Intervention Program (EIP) provides services to persons newly diagnosed with HIV, including medical treatment to prevent or delay the progression of disease, health and treatment education, case management, psychosocial evaluation including counseling and referrals, clinical trial opportunities, and behavior change counseling to prevent the spread of HIV infection to others. The Bridge Program provides for the gradual engagement of HIV-infected persons who are out-of-care into EIP with a specialized outreach to women and disenfranchised minorities. He also runs the one of the two STD clinics from which participants will be recruited for the current study. Dr. Smith will assist with participant recruitment, implementing NAT testing protocols and publishing of study results.

20. BIBLIOGRAPHY

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21. INDUSTRY STUDIES

N/A

22. FUNDING SUPPORT FOR THIS STUDY

This project is funded by contract from the Centers for Disease Control and Prevention (CDC), Contract #200-2007-21016 - IDU Pilot Project.

23. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

24. INVESTIGATIONAL DRUG FACT SHEET

N/A

25. IMPACT ON NURSING STAFF

N/A

26. CONFLICT OF INTEREST

N/A

27. CANCER-RELATED STUDIES

N/A

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

We anticipate that all participants will be capable of understanding our consent form and deciding if they will participate. Our study staff members are trained in informed consent procedures and protection of human subjects. However, to ensure that individuals who are incapable of understanding the consent form are excluded, we will assess participant decisional capacity utilizing the following protocol:

Before a participant signs the informed consent form, staff will thoroughly review the form, ask if the participant understands the content of the consent form, and answer any questions that may arise. Participants will be given a written, unsigned copy of the informed consent form for their records.

The study staff will ask participants to answer three true/false statements at the end of the informed consent form to make sure that they have understood the key elements of voluntary, informed consent and the nature of the study. These statements will include the following:

True/False. All records with your name and information will be kept confidential to the full extent of the law.
True/False. You are free to withdraw from the study at any time.
True/False. The study involves discussions of sex, drug use and other personal things.

If a participant does not answer any of these questions correctly, study staff will review the consent form again and clarify any misunderstandings. The participant will be given three chances to answer the statements correctly. If the participant cannot answer the statements correctly, then he will be considered unable to give voluntary, informed consent and will be disqualified from participation in the study.

APPENDIX A- SCREENER

APPENDIX B – INFORMED CONSENT

APPENDIX C- ASSESMENT