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Study To Assess Hepatitis Risk (STAHR)

Supporting Statement Part B

Statistical Methods
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B. Statistical Methods

1. Respondent Universe and Sampling Methods

Injection drug users (IDUs) within the San Diego County will be the respondent universe for this ICR. Identification of injection drug using individuals is elusive because of the legal consequences of being identified. IDUs also have barriers to health care access because of their distrust of persons in authority. Thus, traditional surveillance systems or population-based sampling would be ineffective for the proposed ICR.

Recruitment site selection for young IDUs like any other hard-to-reach population is a complicated process. Selection of sites for this project was based on knowledge of well-known areas of high drug traffic or drug use or where young injectors are known to congregate, medical services that young IDUs access, and also from mapping through ethnographic methods, through community contacts, key informants and a Community Advisory Board. The selection criteria for the venues where participants will be recruited into this study are expected to 1) provide the most representative sample possible, 2) be feasible for implementation in the heterogeneous venues/methods eligible for conducting the recruitment, and 3) allow for standardized recruitment of 1000 young IDUs during a period of 2 years. Three different recruitment strategies [respondent driven sampling (RDS), active/passive recruitment strategy (street outreach), and venue-based sampling] will be implemented at the venues selected for recruitment by University of California, San Diego.

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%) injected their main drug. While injection drug use is a significant problem and 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. Furthermore, extensive drug use mapping in San Diego followed by successfully recruiting over 500 IDUs using RDS for CDC's 2006, National HIV Behavioral Surveillance (NHBS) IDU survey shows feasibility for this study to be carried out.

<u>Overall sample size</u>

As STAHR is a project to pilot surveillance methods, the number of interviews has been set based on the estimated number of eligible persons, the time available for this pilot project, and the expected level of precision for a random sample. The two recruitment methods (RDS and street outreach method) will each attempt to complete a minimum of 250 interviews and the venue based method will recruit 250 each participants from two different venues (sexually transmitted disease clinic and needle exchange program). If the

project meets the target number of interviews, at least 1,000 young IDUs will be interviewed during the project period.

Because STAHR is mainly descriptive, power calculations, which are used in sample size determinations for testing specific hypotheses, were not performed. Instead, the level of precision, i.e., the estimated 95% confidence interval half-width that can be expected was examined. The expected level of precision for a random sample was calculated for individual recruitment strategies (n = 250). The following table shows the expected level of precision for an estimate from these data, such as, for example, an estimate of the proportion of IDUs for whom heroin is the main drug injected. The CI half-widths in the table are the maximum that would be expected for estimates for total sample sizes of 250. The table below shows the level of precision to be expected not only for estimates for the entire population (column 2), but also for subpopulations (e.g. racial/ethnic groups) that comprise 50%, 25%, 15% and 10% of the total population (column 3, 4, 5, and 6, respectively).

	CI half-width	CI half-width	CI half-width	CI half-width	CI half-width
# interviews	total population	subpopn = 50%	subpopn = 25%	subpopn = 15%	subpopn = 10%
250	6.20%	8.77%	12.40%	16.01%	19.60%

CI half-widths for all the recruitment methods (n = 1000) are not included on the previous table because weighted analyses of the data aggregated across the different recruitment methods may be performed. Weighted analysis of the aggregated data is necessary because the selection probability will not be the same across recruitment methods. Having unequal selection probabilities means that variance estimates obtained from the aggregated sample will be larger than they would be for a simple random sample of the same size. This variance inflation is called design effect.

The following table shows 95% CI half-widths for estimates, given a sample size of 1000 for data from all methods combined. The table shows the level of precision to be expected not only for estimates for the entire population (column 2), but also for subpopulations that comprise 50%, 25%, 15% and 10% of the total population (column 3, 4, 5, and 6 respectively).

	CI half-width	CI half-width	CI half-width	CI half-width	CI half-width
# interviews	total population	subpopn = 50%	subpopn = 25%	subpopn = 15%	subpopn = 10%
1000	3.10%	4.38%	6.20%	8.00%	9.80%

It was decided that the minimum sample size that would be necessary for a project area to obtain total population estimates with an acceptable level of precision was 250.

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The University of California, San Diego (UCSD) who will be implementing the information collection estimates that a convenience sample of 1000 respondents, (with sample sizes of 250 in each of the 4 groups), and an average HCV seroprevalence assumed to be between 0.15 and 0.40 based on existing estimates, a 0.05 significance level Chi-square test will have 80% power to detect a difference in HCV seroprevalence characterized by a variance of proportions between 0.001 and 0.003. Under the assumptions mentioned above, an effect size as small as 0.01 will be detectable. In addition, based on prior research the expected prevalence of high-risk injection practices is assumed to be between 0.30 and 0.75. Given the same assumptions as above this study will have 80% power to detect a difference in risk behavior prevalence across groups of at least 0.01.

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Sampling Methods

Respondent driven sampling methods will be used to recruit 250 participants. RDS provides an opportunity to access potentially hidden populations that may be missed with venue-based sampling. RDS is a chain-referral sampling strategy similar to snowball sampling (Heckathorn, 1997). RDS starts with a limited number of "seeds" who are individuals that meet the study eligibility criteria, complete the study protocol, and are then asked to recruit other eligible individuals from their social networks. They can also be chosen by referrals from people who know the local young injection drug user populations well, or through outreach to areas where young IDUs can be found. Seeds will be asked to recruit a specified number (usually between 3 and 5) of young IDUs they know who meet the eligibility criteria for the study. Respondents recruited by seeds, in turn, complete the survey and are asked to recruit the next wave of respondents, with the process continuing until a target sample size is achieved. RDS will use incentives for participating in the survey as well as for recruiting others.

By starting with a small number of seeds, limiting the number of individuals each participant can recruit, and allowing a significant number of recruitment waves to occur, the distribution of the final sample begins to resemble the underlying eligible population living in the project area and is unbiased by the characteristics of the seeds (Heckathorn, 1997; Heckathorn, 2002). Capping the number of recruits to 5 limits any single individual from dominating the recruitment process. Project staff will track the recruitment process

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using coupons with unique IDs that will be distributed to every young IDU who agrees to be a seed. These unique coupons will be used to link recruiters and recruits.

Each coupon provided to the seeds will have a unique ID and the local project name and location(s) printed on it with a brief explanation of the project. Study coordinators will retain the unique ID number distributed to the recruiters linked to the survey ID. When the coupon is returned by a recruit, the code on the coupon will be linked to 1) the Survey ID of the participant to whom the coupon is issued (i.e., the recruiter) and 2) the Survey ID of the participant returning the coupon (i.e., the recruit). The coupon information is entered and stored in the RDS Coupon Manager.

The RDS Coupon Manager is used 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 met the study enrollment criteria, 6) the new participant's study number, 7) and a 'yes/no' regarding whether incentive was provided to the participant who distributed the coupon. The RDS Coupon Manager 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 two proposed venues are 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 county STD clinic 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.

Active and Passive Recruitment Strategies- Street outreach: At least 250 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 also 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 lube, and educational pamphlets). During these encounters, the outreach worker will also hand out recruitment cards with information about the study. In order to avoid requiring disclosure of the individuals' injection status, they will be told to take the card for themselves or someone they know who injects drugs.

Outreach workers will receive extensive training in how to approach and engage potential participants in these community settings for active recruitment. Ethical guidelines

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regarding professional conduct will be enforced for all outreach workers. Outreach workers will work in pairs in some locations (determined by the sites based on local conditions) 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.

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. 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. When necessary, permission to recruit around business establishments will be secured prior to initiating recruitment.

To recruit for eligibility screening for the baseline questionnaire and blood tests, street recruiters will incorporate locally-developed and proven techniques to engage potential participants in conversation. Each person approached will be given a project recruitment card that provides basic information regarding the study and will be encouraged to go to the study site to be screened for eligibility. Potential participants will be given information about the nature of the study; time involved, and informed that they will receive incentives if they are eligible to and agree to participate. In order to reduce potential embarrassment, the script will include the comment, “If this doesn't apply to you, please give it to someone you know.” The participants will be screened for eligibility for participation when they come to the study site; others may be screened in project vans following recruitment.

Depending on the specific location, and at the discretion of the recruiter, it may be possible to ask potential subjects for personal contact information (name and phone number). Such instances would include a situation in which there is no chance for others in the area to overhear the person's name. 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.

Expected response rates

Response rates using RDS are expected to be between 68% and 76% and based on published reports; CDC and UCSD anticipate that at least one-half to two-thirds of the coupons given to “seeds” will be returned by potential peer participants (Heckathorn, 2002; Johnston, 2006; Ramirez-Valles, 2005; Stormer, 2006; Wang, 2004; Yeka, 2006).

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A benefit of RDS which is a peer-driven sampling is that recruiters are informed about the eligibility criteria so that they can recruit eligible participants. In venue based recruitment, response rates are expected to be similar to other venue based behavioral surveys. For example, participation rate in Drug Users Intervention Trial (not published data) was 83%. Participation rate through the street outreach protocol is expected to be nearly 100%.The overall participation rate is expected to be 80%. Participation rate will be one of the parameters that will be compared among the three different recruitments methods and the results will be used in the decision to select the best method for future surveillance system.

Using ACASI, study participants sit at a computer in a private location away from study personnel and other participants, and respond to questions that appear on the computer monitor and the participant listens to using headphones. This method eliminates the motivation for participants to provide socially desirable responses to sensitive or potentially stigmatizing questions. In our prior studies, including the CDC-funded CIDUS III/DUIT study, we have employed all of these techniques, through which we had very low rates of refusal to answer research questions. Among 3,285 IDUs age 15-30 years-old from five US cities, refusal rates ranged from <1% to <4% for the most sensitive questions on the hour-long baseline assessment. Similar results have been obtained by other IDU researchers. Given that we will employ identical techniques in our proposed pilot study, we expect similarly low refusal rates.

2. Procedures for the Collection of Information

In order to be included in the STAHR 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 testing; 5) agree to provide contact information; 6) not be enrolled in other waves of the study. Following a screener survey, informed consent will be solicited. Those who consent to participate will be asked to complete the survey and will be asked to donate venous blood sample for HCV testing. Potential participants, who demonstrate acute intoxication or behavior impairing their ability to provide informed consent, will be asked to return the next day for screening to participate.

Main steps in data collection

The interviews will be administered using audio-computer assisted self-interview (ACASI) methods. The complexity of the interview instrument—with skip patterns and logic checks as well as the sensitivity of several of the survey questions necessitate a computer-assisted interview. Nevertheless, the eligibility screener portion of the computer-assisted questionnaire will be administered by an interviewer. Using an interviewer to administer the eligibility screener will allow time for STAHR staff to establish rapport with the respondent and to assign a unique ID for the computer assisted survey. RDS should be more successful as a recruitment method when respondents feel comfortable referring their peers to the study staff. However, to improve the likelihood

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of reporting sensitive behaviors the portion of the questionnaire that asks about drug use and sexual behaviors are asked without an interviewer using an ACASI.

Persons recruited using the RDS and street outreach recruitment methods will be asked to make an appointment to take the survey; walk-in hours will usually be available (determined locally) in order to accommodate participants who are willing to complete the survey immediately. When a potential respondent recruited through the RDS comes to the field site, their coupon will be assessed to ensure it is valid, using the RDS Coupon Manager described above. Once the coupon is validated, the interviewer will explain to the potential participant that they are being asked to participate in a health survey, that they will be screened for eligibility first, and that not all persons will be eligible. All persons with a valid coupon will be administered the eligibility screener (Attachment 3). If the referred person is not eligible to participate in this project, he or she will be thanked for their time and interest in the project but will not be interviewed, nor asked to recruit others. If the referred person is eligible to participate in this project, the interviewer will obtain informed consent (Attachment 6). After obtaining consent, the interviewer will instruct the participant on how to complete the survey on the laptop computer; the participant will continue the computer-assisted, self interview. At the completion of the ACASI questionnaire the computer will prompt the respondent to notify the interviewer. The interviewer will then offer pretest counseling about HCV diagnosis prior to drawing blood for HCV testing.

Upon completion of the survey, the pretest counseling, and blood draw for hepatitis C virus infection status determination, the participant will receive incentive for participation in the study and will be asked about contact mechanisms to let her/him know the results of the blood test. The participant recruited in the RDS method will also be asked if s/he would be willing to recruit other participants i.e., become seed. Willing "seed" participants will be offered an appropriate incentive for their participation and will be asked if they are willing to recruit at least 3 other young IDUs in their network.

Participants who agree to recruit their peers will be given a brief training on recruiting their peers. They will also be given three coded, non-replicable coupons which will enable the project to assign the new recruits to the "seed" participant. The participant will be told to give one coupon to each of 3 peers meeting the eligibility criteria. Each coupon will have the local project name and location(s) printed on it with a brief explanation of the project. The code on the coupon will be linked to 1) the Survey ID of the participant to whom the coupon is issued (i.e., the recruiter) and 2) the Survey ID of the participant returning the coupon (i.e., the recruit). The coupon information is entered and stored in the RDS Coupon Manager.

Recruitment using street outreach is expected to be less complicated. Recruitment will be completed by passive methods such as 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. The information that is distributed includes a brief synopsis of the project, eligibility criteria, and contact information for

project staff. Participants will voluntarily present at study site after calling the study coordinator for information regarding specific location to participate in the study.

If eligible, the interviewer will obtain informed consent to participate in the project. After obtaining consent, the interviewer instructs the participant on how to complete the survey on the laptop computer; the participant will continue the computer-assisted, self interview (Attachment 4). At the end of the ACASI questionnaire the computer will prompt the respondent to alert the interviewer. The interviewer will then offer pretest counseling about HCV diagnosis prior to drawing blood for HCV testing.

For the venue based recruitment, study coordinators will recruit young IDUs from two different venues. Based on the estimated number of young IDUs who receive services at these venues the recruitment will include every consecutive eligible person until the desired sample of participants is reached. The two venues include 1) syringe exchange program and 2) sexually transmitted disease (STD) clinics. If respondents are eligible for participation in the survey and consent to participate in the survey, the interviewer will instruct the participants on how to complete the survey on the laptop computer; the participant will continue the computer-assisted, self interview. Participants recruited in the venue based sampling method will not be provided coupons to recruit their peers; however, they are encouraged to talk to their peers to participate in the project.

Quality Control

Data quality is ensured by use of computer-assisted interviewing, interviewer training and monitoring, site visits, and data editing. Computer-assisted interviewing improves data quality in several ways:

a) Interviewer errors are reduced because interviewers do not have to follow complex routing instructions; the computer does it for them.
b) Respondent errors are also reduced. Consistency checks are programmed into the questionnaire so that inconsistent answers or out of range values can be corrected or explained while the interview is in progress.
c) Use of computer-assisted interviewing also reduces coding and coding errors, which makes it possible to prepare the data for analysis faster and more accurately.

A structured training of local field staff will occur prior to implementation of data collection. This training will cover general interviewing skills, the sampling and recruitment protocol, and a question-by-question review of the survey to ensure interviewers understand the purpose of each question and how it should be read and coded in the computer. Interviewers will have opportunities to practice administering the eligibility screener as well as going through the computer-assisted, self interview. The training will also address interviewer integrity, underscoring the importance of collecting quality data and the consequences of inappropriate behaviors, including falsification of data.

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If, during the process of interviewing and data collection, the study team becomes aware of the need for treatment of any participant, referrals shall be made to appropriate medical care providers. Arrangements will be completed for respondents to receive free hepatitis A and B vaccinations if they are eligible for vaccination. Referrals will also be offered for medical treatment and follow up of hepatitis C virus infection if blood test results indicate the results to be positive. The referral will be made after appropriate posttest counseling. Study coordinators and interviewers will be trained regarding issues that commonly arise when working with IDUs including participants high on drugs.

Young IDUs that were recruited using any of the recruitment venues/methods can decline to participate in the project. Those who decline to participate in the project will be informed about locally available support for IDUs and will also be referred for free vaccination of hepatitis A and B.

3. Methods to Maximize Response Rates and Deal with Nonresponse

For respondents recruited using the RDS method, recruiters (seeds) will receive incentives commensurate with the number of recruits with coupons, who are eligible, and agree to participate. All RDS recruits will receive incentives for participating in the study and, offered additional incentives if they serve as peer recruiters or seeds. All participants recruited with any of the methods will receive a $25.00 incentive for participating in the study. All participants will also be tested for HCV infection and will be offered vaccination for hepatitis A and B free of charge. Participants with evidence of HCV infection will be referred for care. These procedures are expected to increase response rates among the participants.

Because RDS is a peer-referral mechanism, the field staff will be able to focus on the recruitment of “seeds”. The unique advantage of RDS is that peer referral and endorsement of the project are likely to have a positive impact on participation rates. The dual incentive structure (i.e., providing incentives to recruiters for successful peer referral) also helps to maximize response rates.

For participants recruited using the outreach method, field site logistics may help to maximize response rates. Field sites will be located in areas that are easy to reach by public transportation and hours of operation will be set to meet the needs and schedules of the population of interest.

4. Test of Procedures or Methods to be Undertaken

The majority of questions for STAHR were developed using questions from previous CDC surveillance projects. Some of the questions will be cognitively tested in the population for which the questionnaire will be used. At the end of the project the participant characteristics at the different recruit methods/venues will be compared for similarities or differences in age, gender, time since initiation of injection drug use,

prevalence of HCV, missed opportunities for diagnosis of HCV, knowledge, attitudes, and practices towards HCV, and take up and completion of vaccination.

Screening of respondents for antibody to hepatitis C virus (anti-HCV) by enzyme immunoassay (EIA) on a serologic sample collected from eligible participants will be carried out at a qualified laboratory selected by the contractor and by the CDC hepatitis reference laboratory. The study coordinator will collect two serologic samples of at least 1.0ml each from consenting eligible participants. Specimen collection will be performed by trained qualified phlebotomists. The consent forms for specimen collection (attachment 6) will clearly detail the adverse events associated with blood draw.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The following senior staff of the Division of Viral Hepatitis was consulted about the statistical aspects of the project, including the sampling strategy, analytic methods for examining the objectives, and sample size.

Richard Garfein, PhD, Associate professor, UCSD
John Ward, MD, Director. Division of Viral Hepatitis, NCHHSTP, CDC.
Steven Wiersma, MD, MPH, Associate Director for Science, Division of Viral Hepatitis, NCHHSTP, CDC.
Deborah Holtzman, PhD, Senior Behavioral Scientist, Division of Viral Hepatitis, NCHHSTP, CDC.
Scott Holmberg, MD, Chief Epidemiology and Surveillance Branch, Division of Viral Hepatitis, NCHHSTP, CDC.
Ian Williams, PhD, MS, Team leader