Teen Alcohol Screening in the Pediatric Emergency Care Applied Research Network (ASSESS)
PECARN Protocol Number 031

Pediatric Emergency Care Applied Research Network
Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program

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PROTOCOL TITLE:

Teen Alcohol Screening in the Pediatric Emergency Care Applied Research Network

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PECARN Protocol Number: 031

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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Alcohol use is a major contributor to the leading causes of adolescent morbidity and mortality and to other health risks, including other substance use and risky behaviors. Adolescent alcohol use may also result in long term cognitive, behavioral, anatomic and neurochemical changes. Additionally, initiating alcohol use in adolescence significantly increases a person's risk for adult alcohol use disorders. Given this considerable public health burden, successfully identifying adolescents at risk for current or future problematic alcohol use is of major importance, as intervention may significantly affect both adolescent and adult alcohol use disorders. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) has developed a novel two-question screening tool for the early detection of alcohol use and problems. Empirically based, the screen may be a powerful predictor of current and future negative consequences of alcohol use. We propose to validate the NIAAA two-question screen with 12-17 year olds in U.S. pediatric emergency departments (PED). The advantage of the PED setting is the ability to capture high risk populations such as school dropouts and those without primary care or insurance, who often use PEDs for their medical care and are missed in other study settings.

Employing the Pediatric Emergency Care Applied Research Network (PECARN), we will use a multi-center design to test the concurrent, convergent and predictive validity of the NIAAA two-question screen using established, validated measurement instruments in a very large, diverse sample of youths. Youths 12-17 years (N=5000) presenting to participating PECARN PEDs will be enrolled over a 3.5-year period and will complete the two-question screen and an alcohol and other drug (AOD) and behavior ("criterion") assessment battery. Responses from these youths will be used to assess the concurrent, convergent, and discriminant validity of the NIAAA two-question screen. Two subsamples of youths will be derived from the initial sample. The first subsample (about 200 participants) will be re-administered the NIAAA two-question screen, one week after their initial ED visit to assess the test-retest reliability of the NIAAA two-question screen. The second sample (about 2225 participants), will be reassessed yearly, for up to 5 years after their PED visit with the criterion assessment battery to assess the predictive validity of the two-question screen. In order to account for attrition, we will assign to follow-up a larger number of participants than the required 1600. This large sample will permit stratified analyses by gender, race, ethnicity and other important demographic variables, which are not possible with single center or smaller sample studies. The research is significant because it rigorously evaluates the ability of the NIAAA two-question screen to predict current and future AOD risks as well as other behavior problems, and will generate very robust, generalizable results.

1 Study Summary

Alcohol use is a major contributor to the leading causes of adolescent morbidity and mortality[1] and to other health risks, including other substance use and risky behaviors. Adolescent alcohol use may also result in long-term anatomic and neuropsychologic changes, and significantly increases ones risk for adult alcohol use disorders [AUD].[2–4] Of further importance, there is recent evidence that the trajectory of alcohol use through adolescence and young adulthood may be prognostic in the development of AUDs.[5–9] Given this considerable public health burden, identifying adolescents at risk for current and future problematic alcohol use is of major importance, as intervention may significantly affect both adolescent and adult AUDs.[10, 11] Accordingly, screening adolescents for alcohol use has been endorsed by numerous medical[12–14] and federal organizations.[15–17] Studies in busy pediatric[18–25] and general[26–31]emergency departments (EDs) have shown that brief screening is feasible and acceptable.

This study will be a large, multicenter, pediatric ED (PED) trial to validate the NIAAA two-question screen. Although the screen has potential utility in a number of settings, the PED is an excellent site for conducting a validation study. Many adolescents infrequently see their primary care provider,[32] and receive their medical care in EDs.[33] In addition to treating a broad cross-section of youth, a PED has the potential to capture high risk youths such as high school dropouts, known to be high risk alcohol users[34] and to frequent EDs.[35]

1.1 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. Determine the concurrent, convergent, discriminant, and predictive validity of the NIAAA two-question screen with respect to alcohol.

Specific Aim 2. Determine the concurrent and predictive validity of the NIAAA two-question screen with respect to other drug use and problem behaviors.

Specific Aim 3. To analyze alcohol-use trajectories in this sample of ED-enrolled youth through the transitions from middle school to high school and from high school to young adulthood. We hypothesize that ED-enrolled youth will demonstrate distinct trajectories of use including stable low use, ascending use, and an ascending/stabilizing trajectory.

1.2   Hypotheses

The primary hypotheses of this validation study are that the screen will accurately *discriminate and predict* drinking frequency, quantity consumed per drinking occasion, frequency of current high volume drinking episodes, alcohol problems, and alcohol abuse or dependence diagnosis. The investigators also hypothesize that the NIAAA two-question screen will converge with results of the Alcohol Use Disorders Identification Test (AUDIT), which is the current gold standard screening tool. The secondary hypotheses are that the screen will accurately predict *current and future* marijuana use, frequency of cigarette use, quantity of cigarette use per typical day, frequency of other substance use, and frequency of problem behaviors.

To determine the variables that predict trajectory class membership, we hypothesize that baseline NIAAA risk category will predict trajectory class membership as well as other predictor variables including gender, mental health symptoms, and risk taking behavior.

1.3   Subject Eligibility, Accrual and Study Duration

Eligible participants will be identified by on-site study staff. Initial screening criteria for inclusion in the study include:

1. youths, age 12-17, inclusive AND
2. who are being seen in the PED for a non life-threatening injury, OR a non life-threatening illness, OR non life-threatening mental health condition; AND
3. the youth, in the opinion of the clinical staff, must be medically, cognitively, and behaviorally stable.

We will exclude:

1. youths who are in severe acute emotional distress, e.g. suicidal, or suspected by the clinical staff of being a victim of child abuse; OR
2. youths who, in the opinion of the clinical staff, are cognitively impaired and unable to give informed assent; OR
3. youths who do not have an accompanying adult who is qualified to give parental permission for the youth's participation in research; OR
4. youths and their parent/LAR who are unable to read and speak English or Spanish; OR
5. those having neither a telephone nor an address of residence; OR
6. those who have already been enrolled in this study.

Youths will be enrolled and will complete the two-question screen and an AOD use and behavior ("criterion") assessment battery. We will enroll an adequate number of participants to achieve 5,000 completed surveys over a 3.5-year period. Two subsamples will be derived from this sample. The first subsample (about 200 participants) will be re-administered the NIAAA two-question screen one week after their initial ED visit to assess the test-retest reliability of the NIAAA two-question screen. The second sample will be enrolled over a 2-year period from PECARN PEDs (about 2225 participants) and reassessed yearly, for up to 5 years with the criterion assessment battery to assess the predictive validity of the two-question screen. In order to account for attrition, we will assign to follow-up a larger number of participants than the required 1600.

2   Rationale and Background

Alcohol use increases throughout adolescence with greater usage rates and escalation occurring in older adolescents. Research has shown that over the course of adolescence, the proportion of youths who have had more than just a few sips of alcohol increases dramatically, from 7% of 12-year-olds to nearly 70% of 18-year-olds.[36]

Nationwide, 36%, 58% and 71% of 9th, 10th and 12th graders, respectively, report lifetime alcohol use.[37] About half of youths 12 to 15 years old and two-thirds of youths 16-20 years old report high volume drinking (defined as five or more drinks per occasion).[36] Current alcohol use, high volume, and heavy drinking rates among US youths ages 12-17 were recently reported as 14.7%, 8.8% and 2.1%, respectively.[36] These rates are especially concerning since the earlier one initiates alcohol use, the more likely they are to experience alcohol-related problems and an alcohol use disorder in later adolescence and adulthood.[38–40] A number of studies have also found strong relationships between alcohol use and other drug use, sex without contraception, delinquency, school failure, and school drop-out.[41, 42]

Adolescent alcohol use and the Pediatric Emergency Department.   Many adolescents infrequently visit their primary care providers[32] and often receive their medical care in Pediatric Emergency Departments (PEDs).[33] As many as 1.5 million adolescents use the nation's emergency departments as their only source of care.[43] These individuals are more likely to report substance use, worse health status and mental health problems,

highlighting a need for PED-based alcohol screening.[44, 45] Further, high school dropouts, who are known to be high-risk alcohol users,[34] frequently use the PED for healthcare.[35] A PED visit may thus represent a unique opportunity to capture high risk adolescents missed in other settings.

Additionally, many adolescents are seen in the PED for alcohol-related events, e.g. car crashes involving alcohol. An analysis of National Hospital Ambulatory Medical Care Survey (NHAMCS) for 2001 through 2004 found that, in the underage drinking population of 13-20 year olds, there were 858,828 alcohol-related ED visits.[46] Although there is a clear advantage to screening youths for alcohol use at both regular and unplanned healthcare visits and intervening as appropriate, current screening tools and intervention strategies challenge the ability of busy clinicians to utilize them.

Two studies conducted in the PED that will serve as the core site in the current study have shown that youths treated in this PED have significant alcohol use rates. Of adolescents 13-19 years treated for an injury in the PED, 62% reported alcohol use within the last year and 18% met criteria for a DSM-IV alcohol use disorder.[47] Another study of adolescents 13-17 years old seen in the PED demonstrated that 29% endorsed some level of drinking and 10% were identified as having alcohol misuse.[48] Others have found similar high rates. For example, in a PED sample of adolescents 11-17 years, 15.8% of patients had a positive Alcohol Use Disorders Identification Test (AUDIT) score.[49]

Screening for alcohol misuse in adolescence. Both medical and federal organizations have recommended screening and behavioral counseling interventions to reduce alcohol misuse and have developed resources to support implementation of these services. These organizations include the American Academy of Pediatrics, American College of Surgeon's Committee on Trauma, American College of Emergency Physicians, Substance Abuse & Mental Health Services Administration, and the Centers for Disease Control & Prevention.[12–15, 17]

While these groups support alcohol screening, brief intervention and referral to treatment (SBIRT), and some have successfully integrated substance use health screening into practice within the PED,[50] at present such screening and interventions are underutilized. In a recent study of US hospitals that treat injured youths, only 18% reported providing universal alcohol screening for their adolescent ED patients.[51] This same study found that 31% of US hospitals surveyed did not use a standardized screening instrument but rather incorporated alcohol questions into their general hospital assessments. Studies have identified lack of time and lack of training/confidence in SBIRT activities as reasons

for low implementation rates.[52, 53] A manageable system for screening and performing brief interventions might significantly contribute to adoption of this approach.

What is the state of the literature on adolescent alcohol screening? Screening patients for alcohol use problems requires the use of standardized questionnaires that are sensitive enough to detect not only patients who have alcohol use, but also those who have alcohol misuse and problems. Although blood alcohol concentrations are easily obtained in a PED, they only detect acute clinical intoxication. Several potential universal screening instruments exist for adolescents including the AUDIT,[54] the CAGE questionnaire,[55] FAST,[56] TWEAK,[57] CRAFFT,[58] DSM-IV 2 item,[59] RUFT-CUT,[60] RAFFT,[61, 62] RAPS4,[63] and a single question regarding binge drinking.[64, 65] Existing instruments are often difficult for busy PED clinicians to administer. In order to be acceptable for use in the PED, universal screening instruments must require minimal training and implementation time. The NIAAA two-question screen, which asks about the patient's drinking frequency and friends' drinking, may be an optimal screening tool for this setting. Drinking frequency represents an empirically supported brief screen to identify adolescents with alcohol related problems.[66] Having substance abusing and deviant peers is linked to adolescents' substance use.[67–70] Some studies demonstrate that the number of alcohol-using friends is the best predictor of an adolescent's alcohol use.[71, 72] Other studies[73] have shown peer influence to have much higher explanatory power for rates of adolescent substance use than school-related prosocial activities have a dampening effect. For this reason asking questions about friends' alcohol use may be an important component of an alcohol screening tool. Analyses of the NIAAA two-question screen indicate that it may be an effective predictor of current and future alcohol problems.[74, 75] While recommended by the NIAAA and American Academy of Pediatrics, this screening instrument requires further testing in clinical settings such as the PED.[76]

How is a screen best validated? Like any measure, screens must follow a standard set of procedures to establish their reliability and then their subsequent validity. The first and most important consideration, overlooked in virtually all studies of adolescent alcohol screens, is a *large representative sample* of adolescents representing the most important demographic characteristics of a population: age, gender, race and ethnicity. Despite the fact that there have been a number of screens tested in the literature, none of the validation studies has had a large or truly representative sample. Newton et al[76] in their review of the literature found 6 studies evaluating 11 adolescent alcohol screens. One (Kelly et al 2009[29]) studied only 18-20 year olds (n=181) and all of the studies collected data on subjects 18 and 19 and some up to age 21. The N in these studies ranged from 103 to 415, and all included adolescents over 18 years old.

This study is unique in its ability to sample an extremely large (almost 12 times larger than the next largest screen study published in the literature) representative sample. Since cut-off scores are often sample-specific,[77] the large representative sample will allow us to examine if cut-offs differ across subgroups based on age, gender, race, and ethnicity, as well as across sites. Sampling from PEDs also allows for a sample of patients with a wide range of alcohol use and alcohol use risk. Thus we will sample adolescents with a wide range of alcohol-use experience — from those with no use to those admitted to the ED due to an alcohol-related event. This should limit the possibility of spectrum bias, i.e. developing a screen on a population with very low use or extreme use which would then not be appropriate for the general population where there will be a range of use. In a prior study conducted in the Brown/Hasbro PED[47] that excluded any alcohol-positive adolescents, 18% of the blood alcohol-negative sample met criteria for an AUD. Because we are including adolescents presenting to the ED with an alcohol-related event, the rates of alcohol use and AUDs should be much higher in the current study.

Second, a screen must be established as *reliable*. Factor structure can be used to help establish reliability but in the case of the NIAAA two-question screener, the number of items precludes such analyses. Most studies have examined the internal consistency of their respective screens, and we will examine inter-item correlations in the two question screen. Only a few studies have examined test-retest reliability.[78–81] This study will examine test-retest reliability as its primary indicator of reliability and will do so with a randomly selected, representative sample, a substantial addition to the literature.

Third, *validity* must be assessed and should include construct validity (convergent, discriminant) as well as criterion validity (concurrent, predictive). Content validity has already been established by the developers of the screen. With respect to discriminant validity, we have added a measure of physical activity that would not be hypothesized to correlate with the NIAAA two-question screen. For concurrent validity, we will calculate sensitivity (ratio of true positives to true positives plus true negatives) and specificity (ratio of true negatives to true negatives plus true positives) with respect to alcohol use diagnoses, which we are using as our gold standard. The predictive validity portion of this project is unique in that the sample will be stratified on age, sex, ethnicity, and race, which will render a robust, representative sample. The follow-up period will be the longest studied to date.

Fourth, *instrument responsiveness*, the ability of an instrument to detect clinically significant change, is another component of validation that is less pertinent to screens

since screens are not typically used as outcome measures in clinical trials. Nonetheless, the large sample in this study will allow us to examine rates of endorsement of screen items across adolescence — 12 to 17 years — which should increase due to naturally increasing exposure to alcohol.

Finally, the large sample available in this project will provide *adequate power* to examine the performance of the screen by age, sex, race, and ethnicity to see if there are subgroup differences based on sociodemographics. In summary, the large representative sample will enable a definitive test of the psychometrics of the NIAAA two-question screen.

Since this diverse sample is one of the largest cohorts of adolescents to be followed longitudinally for alcohol use/misuse, it represents an important opportunity to: 1) examine the long-term predictive validity of the NIAAA two-question screen and 2) examine alcohol-use trajectory during transitions that are known to be critical in the development of AUD: the transitions from middle school to high school, and from high school to young adulthood.

What are gold standards measures against which to validate an adolescent alcohol screen?   It is necessary to identify the gold standard measures against which to validate this new screening tool. With respect to screens, the AUDIT, the most widely used screen for adolescent alcohol misuse, has performed better than the TWEAK and CAGE in screening for problem alcohol use.[47, 82] Two of the validation studies emanated out of the Brown/Hasbro PED.[47, 83] For these reasons, we have chosen the AUDIT as our gold standard against which to measure convergent validity of the NIAAA two-question screen and to compare its predictive validity relative to the NIAAA two-question screen.

To validate the NIAAA two-question screen's concurrent and predictive validity, we also need to determine gold standard measures for assessing alcohol disorders and alcohol problems. Quantity, frequency, and high volume drinking days are standard criteria against which any screen must be compared. The National Institute of Mental Health Diagnostic Interview Schedule for Children IV (DISC IV) is a structured diagnostic interview which assesses more than 30 psychiatric disorders occurring in children, including substance use disorders.[84] This computerized interview is frequently used, is accepted as an appropriate means of establishing a diagnosis short of high intensity training of diagnostic interviewers, and represents the gold standard measure for assessing alcohol abuse and alcohol dependence in several studies validating adolescent alcohol screens.[18, 83] This instrument has demonstrated good to excellent sensitivity (range = 0.73 to 1.0) for psychiatric disorders such as substance use disorder.[85]

3   Significance of Study

This project has public health, clinical and scientific significance. The **public health significance** lies in the fact that it addresses a Healthy People 2020 Objective, specifically, "to increase the proportion of persons who are referred for follow-up care for alcohol problems, drug problems after diagnosis, or treatment for one of these conditions in a hospital emergency department and to increase the number of Level I and Level II trauma centers and primary care settings that implement evidence-based alcohol Screening and Brief Intervention (SBI).[86]" The **scientific significance** of the research lies in its ability to fully address fundamental psychometric questions of reliability and validity because it is fully powered. Evaluating the precision of this instrument in the PED setting will contribute significantly to the pediatric alcohol screening literature. If proven valid and reliable, the data from this study of the NIAAA two-question screen has the potential of being **clinically significant** because it will decrease the amount of time necessary for clinicians to screen youths for alcohol use and alcohol-related problems. Once a clinically validated and manageable screening tool has been identified, such a tool is likely to result in more widespread and accurate screening of youths at clinical visits. The end result of this earlier recognition of youths at risk for alcohol use and those already alcohol-involved may be the initiation of interventions at an earlier point in their alcohol use. Ultimately, successful adoption and integration of such a screening tool into routine clinical care may be a powerful first step towards primary and secondary prevention of adolescent alcohol use.

4   Study Design and Data Collection

4.1   Study Design Overview

This study utilizes pediatric hospitals from the Pediatric Emergency Care Applied Research Network (PECARN) to evaluate concurrent, convergent, discriminative, and predictive validity of the NIAAA two-question alcohol screen. Youths will be enrolled and will complete the two-question screen and an AOD use and behavior ("criterion") assessment battery. We will enroll an adequate number of participants to achieve 5,000 completed surveys over a 3.5-year period. Two subsamples will be derived from this sample. The first subsample (about 200 participants) will be re-administered the NIAAA two-question screen one week after their initial ED visit to assess the test-retest reliability of the NIAAA

two-question screen. The second sample will be enrolled over a 2-year period (about 2225 participants) and reassessed yearly, for up to 5 years with the criterion assessment battery to assess the predictive validity of the two-question screen. In order to account for attrition, we will assign to follow-up a larger number of participants than the required 1600. In addition to validating the two-question screen with respect to alcohol risk, the NIAAA RFA requested evaluation of the two-question screen as "an initial screen for other behavioral health problems, for example other drug use, smoking, or conduct disorder." To achieve this objective, the study will conduct assessments of marijuana use, tobacco use, other substance use, as well as risky sexual behavior and conduct problems with established instruments for adolescents.

4.2   Participant Screening and Enrollment

Screening will occur on a schedule devised by the PECARN DCC (DCC) based on site research staff availability, to ensure that the sample is randomly selected. Qualifying adolescents who meet inclusion/exclusion criteria and their parent(s) will be approached by study staff. The purpose of the study will be summarized, and parents and youths will be given a brief written description of the study to read. Youths who agree to participate in the study will then be asked to provide written assent and their parents will be asked to provide written parental permission.

Recruitment and study procedures will occur during times when the patient and family are waiting to be seen by a PED clinician or during other waiting periods which occur in the course of ED care (e.g. waiting for medical testing to commence and/or the return of testing results, during medication administration, waiting for a procedure or consultation, etc). Current average turnaround time (time from presentation to discharge) for adolescents in PECARN PEDs is 5.75 hours, thus permitting adequate time to complete the questionnaires.

4.3   Participant Confidentiality

The written description for both parent and adolescent and consent and assent forms will note that the adolescent's responses to survey questions regarding AOD use and risky behaviors will be kept confidential. In the event that an adolescent spontaneously discloses suicidal or homicidal ideation/intention/attempt to research staff, the research staff will follow up with the treating physician to discuss the need for breach of confidentiality and options for follow up, per the site's usual practices.

4.4 Study Procedures

Contact Information. After completion of informed consent and assent procedures, the study participant will complete a contact information survey with the research staff containing participant address, home phone, cell phone, email address, and locator information (if assigned to follow-up). This brief online survey will be administered through DatStat^{TM} system. Contact information will be stored separately from participant assessment battery responses.

Concurrent/ Convergent/Discriminant Validity Procedures. The study participant, with the help of the research staff, will complete questions regarding parent education and parent occupation. The study participant will complete the NIAAA two-question screen and the criterion assessment battery. The entire assessment battery will be administered as bilingual audio computer-assisted self-interviewer (ACASI) web-based surveys. An online DatStat^{TM} survey system on tablet computers will be utilized for this data collection. The ACASI method permits confidential assessment which has been shown to increase the veracity of self-reported data on sensitive topics. For purposes of confidentiality, parents will be asked to leave the room while the adolescent completes the measures. However, there may be times that the parent is reluctant to leave the teen and in those cases, we will still be able to collect the data because the ACASI procedures will help ensure confidentiality. In addition, as part of the assent/consent process, it will be made clear to both the youth and the parent that the youth's responses to the questions will not be shared with the parent. However, the parent will be informed if the child spontaneously discloses to the research or medical staff that they will harm themselves or others or reports abuse. Participants will also be told they can skip questions they do not wish to answer and they can end their participation in the survey at any time.

Due to the exceptionally busy nature of the PED environment, we have designed our assessment battery to be concise and easy to administer. Administration of the questionnaire can be interrupted or paused if medical care is needed, and resumed when the episode of medical care is completed. Most participants will be able to complete the questionnaire within 20-40 minutes (depending on level of substance use). Although the assessments will be in self-report format, the research staff will remain nearby to clarify issues or answer any questions that may arise. These procedures are designed to minimize interference with PED care and patient flow, and have been successfully utilized by the research team in previous PED studies[87, 88] and numerous other PED studies of AOD screening and/or intervention.[18, 29, 48, 60, 83, 89–91]

The procedures are identical for the convergent, discriminant and concurrent validity portions of the study. The AUDIT will be the measure against which convergent validity will be assessed, and the YRBS Physical Activity Section will be used for discriminant validity. The other measures, also described below, will be used to assess concurrent validity.

Assessments. Assessment instruments will be kept together as item sets except when skip patterns dictate otherwise. For the NIAAA two-question screen, we will adhere to the screening protocol detailed in the *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*.[92]

Five possible outcomes will be numerically coded for responses to the two-question screen as follows:

- (0) Nondrinker, friends don't drink;
- (1) Nondrinker; friend(s) do drink;
- (2) Drinker – Lower Risk;
- (3) Drinker – Moderate Risk;
- (4) Drinker – Highest Risk.

In order to control for question order effects, the assessment battery measures will be delivered in random order by creating six differently ordered assessment battery protocols in DatStat^{TM} that will be randomly selected.

The **AUDIT** is a commonly used youth screening tool for alcohol-related behaviors. It is recommended as an additional resource by the NIAAA *Alcohol Screening Practitioner's Guide*.[92] The AUDIT is a 10-question screen focusing on the quantity and frequency of alcohol use, alcohol dependence and alcohol related consequences[54] and has an established internal consistency of alpha = .85 (consumption) and .61 (consequences).[83] The AUDIT has performed better than the TWEAK and CAGE in screening for problem alcohol use.[47, 82]

The **DISC** uses DSM-IV criteria and is the most widely used and studied mental health interview that has been tested in both clinical and community populations.[84] It is considered appropriate for youths age 9 to 17 years. The DISC has been used in a number of ED screening studies[18, 83] and thus we will be able to compare our findings to previous data. In addition, the DISC has been shown to have high sensitivity (.73-1.0 for psychiatric disorders such as substance use disorder)[85] and we have set the cost/benefit

ratio high, reasoning that the risk associated with not correctly identifying an adolescent with alcohol problems (false negatives) is higher than misclassifying an adolescent without alcohol problems (false positives). Thus, the DISC provides a diagnostic interview with high sensitivity. The software will be programmed such that we will also be able to obtain DSM-5 diagnoses based on the currently proposed additional questions for the alcohol use disorders in DSM-5.

The **Reckless Behavior Questionnaire (RBQ-R)** is a brief scale that assesses past year risky behavior.[62] This scale has internal consistency of .80.[62] Selected items from the RBQ will be administered to assess risky sexual behavior (sex without birth control, casual sex) and antisocial behavior (property destruction, shoplifting). RBQ items pertaining to drug use will not be administered since they are covered elsewhere. Also, the driving questions will not be used as a large portion of our sample will not yet be of driving age and driving laws vary by state.

The **Youth Risk Behavior Surveillance System (YRBSS) physical activity section** questions will be used to assess discriminate validity. This six scale measures participation in physical activity, physical education classes, sports teams and time spent watching/using the computer or playing video games.

The **Drug Use Questionnaire** assesses the number of days in the past 30 days teens used nicotine, marijuana, cocaine, LSD, PCP, inhalants, etc. Internal consistency in Co-PI Spirito's ED sample (Spirito et al 2004) was .75 (alpha = .80 when inhalants was dropped). Test/retest for mean number of days each substance was used was .83 from 3 to 6 month follow-up and .94 from 6 to 12 month follow-up.

Newton et al 3 Question ED Screening Tool is a newly recommended screening tool consisting of a 2 question instrument for detecting youth alcohol misuse (derived from DSM-IV criteria for detecting probable alcohol misuse) and a 1 question instrument for detecting marijuana misuse (derived from DISC).[76]

The **CRAFFT** (Car, Relax, Alone, Forget, Friends, Trouble) one screening option often utilized for adolescents, has been found to be a valid screening tool with acceptable sensitivity and specificity for adolescent substance-related problems[93]

The **GAIN** (Global Appraisal of Individual Needs) is a well validated screen for adolescents and adults to quickly and accurately identify clients who have one or more behavioral health disorders (e.g., internalizing or externalizing psychiatric disorders, substance use dis-

orders, or crime/violence problems). The conduct disorder subscale will be administered.[94]

The **MHI-5** (Mental Health Inventory-5) will be administered to measure mental health status. The MHI-5 is well validated and general mental health status will be measured with an item assessing general health.[95]

Demographic information (age, gender, race, ethnicity, and grade) will also be collected from participants at baseline.

Test-Retest Reliability Procedures. A random sample of about 200 enrolled subjects will be contacted by phone after one week to complete the NIAAA two-question screen for a second time, to permit assessment of test-retest reliability of the two-question screen. Consent/assent forms from all sites will be written to say that participants may or may not be asked to participate in the test-retest assessment. Participants must be contacted within 7-14 days in order to have their data included in the test-retest analyses.

About 200 participants will be randomized to the test-retest group immediately following completion of the baseline assessment. If assigned to the test-retest group, participants will be told to expect contact from the research team in one week. The contact will serve as a reminder to test-retest participants who will then be sent a link to permit completion of the screen online via DatStat^{TM}. For participants without Internet access, test-retest follow-up will be conducted by phone by the research team at Brown /Hasbro, who will be blind to baseline responses.

This will ensure a consistent approach to the collection of these data and places no additional burden on participating sites beyond enrolling subjects, administering the baseline assessment, and collecting contact information.

Predictive Validity Study Procedures. A separate random sample of about 2,225 youths who enroll in the main (concurrent validity) study at these sites will be contacted yearly, for up to 5 years following their PED visit to assess the predictive validity of the two-question NIAAA screen. Consent/assent forms will be written to say that participants may or may not be asked to participate in the follow-up. Participants may be assigned to the test-retest group AND the predictive validity group. If assigned to the predictive validity group, at the follow-up points, youths will complete the NIAAA two-question screen and the criterion battery administered at baseline and at the follow-up points using the web-based DatStat^{TM} software. For participants without web access, follow-up assessments by phone will be conducted by the research team at Brown /Hasbro. For

those participants who may turn 18 prior to this survey, a waiver of documentation of informed consent is requested, given the minimal risk of the survey materials.

For participants who did not consent/assent to additional follow-up procedures after the 24 month follow-up (as this study procedure was added at a later date), we will ask their permission to participate in future follow-up surveys one of two ways. Either they can select yes at the end of the 24-month follow-up survey to be contacted in the future to answer similar survey questions or Hasbro Children's Hospital research staff will contact the participant via mail and/or telephone (based on current available information) to confirm if they would like to participate in the same procedures as the other surveys. The parent will also receive notification about their teen's option to extend their participation with the option to remove them from the study, if desired.

4.5   Recruitment Estimates and Attrition

Recruitment sample estimates.   It is projected that 1,715 study-eligible adolescents per week will present to the enrolling PEDs during the 42-month concurrent/ convergent/discriminant validity enrollment period (a total of 312,137 eligible adolescents over 42 months). Site research staff will recruit participants readily permitting enrollment of up to 10 participants per week at each participating site, thus allowing enrollment of an adequate number of participants to achieve 5,000 completed surveys over the enrollment period for the concurrent/convergent/ discriminant validity study. In previous studies at the main investigator's institution (which involved much lengthier questionnaires), 85% of the eligible families who were approached agreed to enroll in the study. Thus, this enrollment projection is feasible.

A unique facet of this study will be the ability to designate recruitment targets, at a wide array of geographic sites, by age, sex, ethnicity, and race to ensure a diverse sample so that the validation of the screen can be optimal. Given the diversity of the participating PECARN sites, we do not anticipate any problem recruiting large numbers within most demographic groups, determined by age (12-13, 14-15, 16-17), gender (male, female), ethnicity (Hispanic, non-Hispanic) and race (black, white). A large number of Asian participants and some American Indian/Alaska Native and Native Hawaiian/Pacific Islander participants will allow some, albeit less robust, conclusions about these groups.

Protection against attrition.   Several different mechanisms will be used to keep participants in the predictive validity arms of the study engaged in the study's follow-up activities. Prior to the follow up surveys, the participant will receive reminders which provide them with the dates the survey is open, how to access the web-based survey,

project contact information for any questions. Reminders will also be sent to parents.

In addition, at enrollment, parents will be asked to identify an individual to serve as a locator, if their child is randomized to the long term follow-up group. The locator will be contacted only if all efforts to reach the youth with the provided information failed. These methods have been used in previous studies, and have achieved successful follow-up rates with our teen participants. At the time of the PED visit, the importance of confidentiality as it pertains to these follow-up assessments will be discussed with youth and parents, and parents will be asked to agree to the confidentiality arrangement previously stipulated.

Compensation.   Participants may be compensated for the time it takes to complete the baseline ($10), 1-2 week ($5), and long-term ($25) follow-up assessments as approved by each site's Institutional Review Board (IRB).

5   Data Analysis

The primary hypotheses of this validation study are that the screen will accurately *discriminate and predict* drinking frequency, quantity consumed per drinking occasion, frequency of current high volume drinking episodes, alcohol problems, and alcohol abuse or dependence diagnosis. The investigators also hypothesize that the NIAAA two-question screen will converge with results of the Alcohol Use Disorders Identification Test (AUDIT), which is the current gold standard screening tool. The secondary hypotheses are that the screen will accurately predict *current and future* marijuana use, frequency of cigarette use, quantity of cigarette use per typical day, frequency of other substance use, and frequency of problem behaviors.

To determine the variables that predict trajectory class membership, we hypothesize that baseline NIAAA risk category will predict trajectory class membership as well as other predictor variables including gender, mental health symptoms, and risk taking behavior.

5.1   General Analytic Issues

Sample representativeness and data imputation.   We will monitor limited demographic summaries of those who do not agree to participate to determine whether we are capturing a sample that is a reasonable representative of each site's population. Post-inclusion attrition will be examined by comparing follow-up assessment completers and non-completers on socio-demographic and baseline data to determine if there are

systematic differences. We will perform analyses by subgroups to examine the role of age, sex, race, and ethnicity in influencing the overall sample validation results. Similarly, subgroup analyses will evaluate whether performance of the screen differs by site beyond expected differences based on the variability in socioeconomic, ethnic and racial differences across sites.

Missing data. If there are significant fractions of missing data, multiple imputation will be used under the assumption that data are missing at random (MAR).[96] There is a distinction between *completely random drop-outs* (independent of phenotype or covariate, missing completely at random [MCAR]), *random drop-out* (drop-out may depend upon past measures, but is not dependent on what the measure would have been at the time of missed assessment, MAR) and *informative drop-out* (may depend on prior variables and on state at possible time of missed assignment).[97, 98] In the case of informative drop out, standard methods of multiple imputation[98, 99] will be used for variables where unplanned missingness is an issue. We will also conduct sensitivity analyses that count all subjects lost to follow-up as having initiated alcohol use or, if the subject was drinking at the prior assessment, either maintaining or initiating high volume drinking. If the results are similar with and without extreme missing data assumptions, confidence in the findings increases.

Transformation of individual question responses. Whenever the question about number of drinking days (Question 1 for high school ages and Question 2 for middle school ages) is analyzed separately, two versions of the analysis will be performed. The first will use the actual frequency responses. These data are likely to be skewed and will be transformed as necessary. The second will transform younger children's responses to a 17-year-old equivalent based on the increased risk at younger ages. For example, one drinking day per year for a 15-year-old could be considered approximately the same as six drinking days per year for a 17-year-old [cf. *Alcohol Screening & Brief Intervention for Youth: A Practitioner's Guide*, p.20].

5.2 Specific Aim Analyses

Specific Aim 1. Determine the concurrent, convergent, discriminant, and predictive validity of the NIAAA two-question screen with respect to alcohol.

We will calculate test/retest *reliability* of the two-question screen using the intraclass correlation coefficient (ICC). This will be performed both for the overall index as well as for each individual question. For high school ages, a correlation between the two questions

will be calculated as another measure of consistency. For middle school ages, a summary of the distribution of Question 2 responses will be given for each value (yes/no) of the responses to Question 1.

To determine *concurrent validity* of the NIAAA two-question screen, we will compare the outcome on the NIAAA screen and responses to individual questions of the NIAAA screen with responses to criterion assessments (AUDIT, DISC, and RBQ-R), as detailed in Section 4.4 on page 18.

The two-question screen overall alcohol-use risk index will be compared to the five-level ordered categorical AUDIT criteria of quantity per drinking episode, frequency of drinking, and high-volume drinking by comparing the distribution of criteria values between each level of alcohol-use risk (0 through 4). The Wilcoxon rank-sum test will be used to compare level 0 to 1, 1 to 2, 2 to 3, and 3 to 4 to test for an increasing trend. In a sub-analysis, responses to Question 1 and, for high school ages, Question 2 will be compared to these three criteria by dichotomizing the question responses at the median and comparing AUDIT criteria values of the groups above and below the median using the Wilcoxon rank-sum test.

We will perform *receiving operator characteristic* (ROC) analysis on the diagnostic outcomes of the DISC (abuse and dependence), using the two-question screen index at each of the possible cut points. *Sensitivity, specificity, and predictive values* will be reported for each cut point, overall ROC curve will be plotted, and optimal cut points will be determined. In addition, levels of the two-question screen index will be compared between alcohol abuse diagnosis (yes/no) and between alcohol dependence diagnosis (yes/no) using the Wilcoxon rank-sum test. The distribution of individual screening questions will also be compared between groups defined by the dichotomous DISC diagnoses.

Discriminant validity will be determined using physical activity questions from the Youth Risk Behavioral Surveillance System.

To determine the *convergent validity* of the NIAAA two-question screen, we will compare the outcome on the NIAAA screen to the overall alcohol risk assessment on an alcohol screening instrument frequently used with youth in the PED setting, the AUDIT. We will compare the distribution of the AUDIT risk scores at each level of the two-question screen outcome. This will be done using both the Wilcoxon rank-sum test and ANOVA with a post-hoc test for increasing trend. The AUDIT scores will also be dichotomized using a cut point of 4 and above. We will perform ROC analysis of this dichotomous outcome using the two-question screen to predict. We will also investigate other possible

cut points for the AUDIT risk score. Associations with the individual screen questions will also be studied using methods similar to those that have been described.

To determine the *predictive validity* of the NIAAA two-question screen, we will re-administer the two-question screen and the criterion assessment battery yearly, for up to 5 years after the initial assessment. Outcomes will be assessed at each follow-up point using the following as gold standards: quantity/frequency on the AUDIT, and the DISC alcohol modules for "abuse" and "dependence". Using a scheme similar to Knight et al.,[100] based on the results of the criterion battery (specifically the DISC and age-appropriate cutoffs for the AUDIT), participants will be classified into one of five categories: nondrinkers, non-problem drinkers, problem drinkers, alcohol abusers, and alcohol dependent. For the purpose of the sensitivity and specificity determination, criterion battery responses will be dichotomized into "problem drinker or worse" and "not problem drinker" (nondrinkers and non-problem drinkers). All assessments of concurrent and convergent validity will be repeated for this analysis using follow-up data.

Specific Aim 2. Determine the concurrent and predictive validity of the NIAAA two-question screen with respect to other drug use and problem behaviors.

The concurrent and predictive validity analyses for other drug use follow the same analytic plan as the corresponding analyses for alcohol use outcomes described above.

The analyses described above for the primary and secondary aims will also be performed on subsamples based on age, gender, race, and ethnicity. We will also perform these analyses on random subsamples to check consistency of results to help rule out, for example, a scenario where a small proportion of individuals is driving the results.

Specific Aim 3. To analyze alcohol-use trajectories in this sample of ED-enrolled youth through the transitions from middle school to high school and from high school to young adulthood. We hypothesize that ED-enrolled youth will demonstrate distinct trajectories of use including stable low use, ascending use, and an ascending/stabilizing trajectory.

To determine the variables that predict trajectory class membership, we hypothesize that baseline NIAAA risk category will predict trajectory class membership as well as other predictor variables including gender, mental health symptoms, and risk taking behavior.

We will use latent growth mixture models (LGMMs) to identify distinct alcohol-use trajectories.[101–103] These models allow for identification of unobserved subgroups

within the population that follow particular trajectories. They can also be used to uncover variables that predict trajectory class membership. Drinking frequency will be the dependent variable. We will begin with a small number of classes and add potential classes, evaluating each model with model-fit indicators, such as Akaikes Information Criterion (AIC), until the optimal number of trajectory classes is identified. We will then add predictor variables to the model and test for their associations with the trajectories.

5.3 Sample Size Calculations and Statistical Power

Evaluating the validity of the two-question screen involves several analyses. Test/retest with a representative sample of about 200 will allow us to determine whether there is a stable correlation of 0.90 or higher, which would indicate excellent test-retest reliability. We have used ROC analysis and, in particular, sensitivity as the basis for our sample size requirements. If we assume a target sensitivity of 90%, and a goal of as low as $\pm$ 2.5% for the corresponding 95% confidence interval, we need approximately 550 children to be positive for the outcome of interest. Conservatively extrapolating from data reported by Knight et al.[104] and Chung et al.,[47] we use the indicator of problem use or worse as the outcome of interest for sample size purposes and estimate that approximately 4% of younger children (12-14) and 18% of older children (15-17) will fall into this category. If half of the subjects enrolled fall into each of these age groups, approximately 5000 subjects will be needed in order to observe the required number of positives.

Predictive validity will be evaluated in a subset of subjects. We have a goal of as low as $\pm$ 4.8% for the 95% confidence interval around sensitivity, which is again assumed to be 90%. This will require approximately 176 children who are positive, or a total of approximately 1600 children enrolled. Approximately 20% attrition is expected, however, so 2225 will be enrolled in the predictive validity component of this study.

6 Data Management

6.1 Clinical Sites

The primary risk involved in participation in the study is breach of confidentiality. Consequently, all subject information will be referenced to a subject ID number, which can be connected to the patient's name through a master file, accessible to senior research staff only. All local research records will remain in a locked file in a secure room unless being used by research staff, and all computerized information will be maintained on password protected computers.

6.2   EMSC Data Coordinating Center (Utah)

In addition to locally secured, identifiable information, partially identifiable information for all sites will be maintained at the PECARN DCC (DCC), located at the University of Utah in Salt Lake City, Utah. The DCC has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, and separate air filtering. The server facility is locked separately from the remainder of the DCC and access to the building is monitored by security personnel year round. The DCC coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the DCC with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University.

Network equipment includes three high-speed switches and two hubs. User authentication is centralized with two Windows 2003 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using SSL or VPN technologies, both of which provide at least 128 bit encryption. OpenClinica (Web-based clinical studies data management system), eRoom^{TM} (Web-based collaborative workspace) and other web applications use the SSL protocol to transmit data securely over the Internet. Direct access to DCC machines is only available while physically located inside the DCC offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts.

Servers are backed up daily through a dedicated backup server that connects across an internal Gigabyte network to a robotic tape drive. Incremental backups occur hourly Monday through Friday from 6am to 6pm. Incremental backups are also performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the server room, and full backups are taken off site on a weekly basis. These backups are encrypted. Security is maintained with Windows 2003 user/group domain-level security.

Users are required to change their passwords every 90 days, and workstations time out after 10 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server. All portable computers are whole-disk-encrypted.

6.3 Survey Data Collection

Participants will complete surveys through DatStat^{TM}, a secure web based survey program. DatStat^{TM} maintains extremely stringent levels of encryption and data storage. The technology platform including servers, database, and web presences that employ multiple forms of security features to protect data and the participants involved in data collection efforts. All DatStat^{TM} servers used for data collection are highly fault-tolerant and are equipped with redundant, hot-pluggable power supplies, redundant network interfaces, and RAID 1/5 hot-pluggable disk storage. All primary servers are plugged into a monitored uninterruptible power supply (UPS) offering a minimum of 30 minutes of battery power in the event of a power outage. At least one additional server is available at all times to handle the off-chance of a major server crash.

DatStat^{TM} secure servers are registered with site certificates provided by VeriSign Internet Trust Services that provides for advanced encryption over the wire. As users move through the data entry forms, the responses are encrypted while in-transit between the browser and the DatStat^{TM} server using SSL (Secure Sockets Layer) and 128-bit Public Key Encryption. DatStat^{TM} servers are stored in a locked, well-ventilated room in locked server cabinet/racks. The server room is in a building with 24/7 alarm security.

Protection of servers from remote attacks is accomplished with a dedicated hardware Watchguard firewall with auditing enabled at the recommended settings. Watchguard LiveSecurity keeps DatStat^{TM} IT staff advised of all known security alerts. The firewall ensures that all traffic is closely monitored and suspicious packets blocked from access to the production systems. Security patches are applied to DatStat^{TM} servers on a timely and ongoing basis. Logs are created by the web servers to increase accountability and are essential in investigating incidents after the fact. The following are logged: failed and successful logins, attempts to access files/directories without authority, successful and failed attempts to access sensitive data.

DatStat^{TM} SQL Server database backups are conducted by DatStat^{TM} on a daily basis. Backups are encrypted and streamed to a secure offsite location. Backups are encrypted using 256-bit AES encryption. Physical access to servers and data backup is also restricted to a minimal number of DatStat^{TM} IT professionals. Such access is provided only with strong passwords that regularly expire. Access to data stored in the server is available only to designated DatStat^{TM} users who log in with specified usernames and passwords.

6.4   Data Confidentiality

Because of the potential legal implications of adolescent high risk behavior (e.g., illicit AOD use), a Certificate of Confidentiality will be obtained from the U.S. Department of Health and Human Services for this study. Participant confidentiality will be breeched only to protect the safety and welfare of research participants and only in accordance with state and federal law.

Adolescents and parents will be made aware of this policy at the commencement of their involvement in the study. Also, at the conclusion of the long term follow-up assessment surveys, participants will be provided with a link to the on-line SAMHSA treatment locator.

The PI and other research personnel have all completed training and received certification in Human Subjects Research Protection and HIPAA. All project staff hired will also successfully complete this training prior to engaging in any research or treatment with study participants and renew this training as required by their institution.

The investigators and staff of the DCC are fully committed to the security and confidentiality of all data collected for PECARN studies. All DCC personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

The staff, reviewers and investigators involved with this study will be required to sign agreements from the DCC that relate to maintenance of passwords, information system security, and data confidentiality.

6.5   Data Quality Management and Monitoring

The DCC monitors PECARN studies on behalf of the investigators and the funding agency. The purposes of monitoring include demonstration of adherence to human subjects protection requirements and assurance of high quality study data. Monitoring is usually done remotely and may also involve physical site monitoring visits.

Site monitoring visits: Site monitoring visits may be conducted during the study to review patient safety and to assure regulatory compliance. The site monitoring visits would include an on-site meeting of the monitor, the HEDA investigator and his/her staff. The primary purpose of site monitor visits is to review compliance with the study methodology and adherence to Good Clinical Practice guidelines. The site monitor will

provide each site with a written report and sites will be required to follow up on any deficiencies.

6.6   Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives of the National Institutes of Health, and the Institutional Review Board (IRB) for each study site, if appropriate.

7   Protection of Human Subjects

Institutional Review Board (IRB) Approval   The DCC and each clinical center must obtain approval from their respective IRB prior to participating in the study. The DCC will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

Potential Risks and Benefits: The primary risk of this study is loss of privacy and breach of confidentiality of the subject. This is mitigated by data security procedures described for our information systems. There are no likely benefits from participation in this minimal risk study, but there is potential benefit to others because of the knowledge that may be gained from this research.

Informed Consent: All subjects will be informed of the purposes (i.e. knowledge and use of counseling strategies for substance abuse) and procedures of the study. Patients at baseline will be consented and assented as previously discussed. For patients who may turn 18 prior to a test-retest or long term follow-up survey, a waiver of documentation of consent is requested, given the minimal risk of the survey materials. The electronic survey will contain all of the elements of consent on its opening page.

Data and Safety Monitoring Plan Although this study poses minimal risk and is not a clinical trial, we have created a system for oversight of the project. Dr. Linakis (PI), other senior investigators, and the PI of the DCC (Dr. Dean) will conduct regular oversight of participant safety. They will review participant progress, including any protocol violations as reported to local site IRBs.

Any planned or unplanned breaches of confidentiality will be reported to the DCC and reviewed by Dr. Linakis (PI), other senior investigators, and the PI of the DCC (Dr. Dean) to determine whether there is a need to alter procedures.

8 Health Insurance Portability and Accountability Act

The abstracted data will be de-identified with respect to patient identifiers. Dates will be recoded to provide the age, and the DCC will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All study sites have been or will be offered Business Associate Agreements (BAA) with the University of Utah. Copies of signed BAA are maintained at the DCC.

9 Inclusion of Women and Minorities

The gender, ethnic and racial composition of patients enrolled in all PECARN studies is a function of the underlying referral population at each Clinical Center selected by the Maternal and Child Health, Emergency Medical Services for Children (EMSC) Program to participate in the network. There will be no exclusion of patients based on gender, race, or ethnicity.

10 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

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