Emergency Department Screen for Teens at Risk for Suicide (ED-STARS) PECARN Protocol Number 033

Pediatric Emergency Care Applied Research Network
National Institute of Mental Health (NIMH)

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This protocol is PECARN Protocol Number 033, and has been authored by Cheryl King, Ph.D, ABPP (University of Michigan), Jacqueline Grupp-Phelan, M.D., MPH (Cincinnati Childrens Hospital Medical Center), & David A. Brent, M.D. (University of Pittsburgh Medical Center) for implementation with the PECARN investigators. This study is supported by 1U01MH104311 awarded to University of Michigan [PI: Cheryl King, Ph.D, ABPP (University of Michigan), Jacqueline Grupp-Phelan, M.D., MPH (Cincinnati Childrens Hospital Medical Center), & David A. Brent, M.D. (University of Pittsburgh Medical Center)] by National Institute of Mental Health (NIMH).

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PROTOCOL TITLE:

Emergency Department Screen for Teens at Risk for Suicide

Short Title: ED-STARS
PECARN Protocol Number: 033

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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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Nomenclature

AE: Adverse Event

ASQ: Ask Suicide-Screening Questions

AUC: Area Under the Curve

CAB: Community Advisory Board

CAD: Computerized Adaptive Diagnosis

CAS: Computerized Adaptive Screen

CAT: Computerized Adaptive Testing

CFR: Code of Federal Regulations

CoI: Conflict of Interest

DCC: Data Coordinating Center

DSM: Diagnostic and Statistical Manual of Mental Disorders

DSMB: Data Safety Monitoring Board

ED-STARS: Emergency Department Screen for Teens at Risk for Suicide

ED: Emergency Department

EDB: Essential Documents Binder

EDCS: Electronic Data Capturing System

EMSC: Emergency Medical Services for Children

GCP: Good Clinical Practice

HIPAA: Health Insurance Portability and Accountability Act

IAT: Implicit Association Test

IOM: Institute of Medicine

IRB: Institutional Review Board

IRT: Item Response Theory

LR: Likelihood Ratio

MDD: Major Depressive Disorder

MedDRA: Medical Dictionary for Regulatory Activities

NIH: National Institute of Health

NIMH: National Institute of Mental Health

NPV: Negative Predictive Value

NSSI: Non-Suicidal Self-Injury

OADR: Office of the Associate Director for Clinical Research

OD: Office of the Director

OHRP: Office for Human Research Protections

PECARN: Pediatric Emergency Care Applied Research Network

PI: Principal Investigator

PPV: Positive Predictive Value

QALY: Quality Adjusted Life Years

RA: Research Assistant

RC: Research Coordinator

ROC: Receiver Operator Characteristics

SA: Scientific Administrator

SAE: Serious Adverse Event

SAN: Storage Area Networking

SRC: Survey Research Center

SSL: Survey Service Lab, Secure Socket Layer

VPN: Virtual Private Network

Abstract

In this multi-site project we will implement two, sequential studies with the overall goal of identifying youth at risk for suicide in the Emergency Department (ED). We will enroll eligible youths, ages 12 to 17 years. In Study 1, we will implement a universal suicide risk assessment using a broad range of risk factors with approximately 6,900 youth, ages 12 to 17. We will follow-up a subsample of approximately 43% of these youth, enriched for suicide risk factors, at 3 and 6 months with interviews. Medical chart reviews will be conducted for the subsample of participants selected for follow-up as well as an additional subsample of about 1,000 youth who will be randomly selected from the remaining study sample. Based on the risk data gathered, we will develop and calibrate a Computerized Adaptive Screen (CAS) to accurately predict suicide attempt. In Study 2 we aim to validate the specificity and sensitivity of the CAS and ASQ for predicting suicide attempts, and to evaluate the performance of the Implicit Association Test (IAT), controlling for CAS and ASQ scores. In Study 2, we will recruit a new sample of approximately 4,000 youths (stratified by suicide risk factors), administer the CAS, the Ask Suicide-Screening Questions (ASQ), a brief survey assessing other suicide risk factors, and the Implicit Association Test-Suicide (IAT-S). We will follow-up at 3 months with interviews. We will also follow-up at 6 months with youth and parent (youth <18 yrs) interviews for the first approximately 2,000 subjects enrolled in Study 2. Medical chart reviews will also be completed for youth enrolled in Study 2.

The study will be conducted with the Pediatric Emergency Care Applied Research Network (PECARN) and the Whiteriver PHS Indian Hospital ED (Whiteriver). PECARN is designed to support large prospective studies with a strong research infrastructure and an established Data Coordinating Center (DCC). The goal of PECARN is to conduct high priority multi-institutional research into the prevention and management of acute illnesses and injuries in youth across the continuum of emergency medicine health care. The Whiteriver PHS Indian Hospital is participating as a site in this study because the prevalence rate for suicide deaths is substantially higher among American Indian youth than among any other racial/ethnic subgroup of youth in the United States.

1 Study Summary

1.1 Hypotheses

The hypotheses of this study are:

1. We hypothesize that the CAS will outperform the ASQ with respect to accuracy of prediction of suicide attempts.

2. We hypothesize that the IAT will add incrementally to the prediction of suicide attempts above and beyond CAS and ASQ scores.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. To develop an optimal suicide risk screen for youth presenting to the emergency department (ED). We will develop a personalized, computerized adaptive screen (CAS) and compare its psychometric properties (e.g., sensitivity, specificity, positive and negative predictive value) for predicting one or more suicide attempts to those of the Ask Suicide-Screening Questions (ASQ).

Specific Aim 2. To develop and validate a parsimonious CAS algorithm for risk stratification of youth to "high risk for suicide attempt" (high probability), "at risk" (need for mental health referral but no high risk) and "low risk" (low probability, no need for mental health referral) groups.

Specific Aim 3. To validate the CAS personalized suicide risk screen prospectively, examining its sensitivity and specificity for the 3-month and 6-month prediction of suicide attempts.

Specific Aim 4. To determine if the IAT adds incrementally to the prediction of suicide attempts above and beyond CAS and ASQ scores.

1.3 Subject Eligibility, Accrual and Study Duration

Inclusion criteria are:

1. Patients ages 12-17 years, inclusive.

We will exclude subjects with any of the following:

1. Patients who are wards of the State; OR
2. Patients previously enrolled in this protocol; OR
3. Patients who are non-English speaking; OR
4. Patients who are medically too unstable to participate; OR
5. Patients with cognitive impairment that will interfere with conducting the study; OR
6. Patients with a same parent sibling who is already enrolled in the study.

Eligible patients will be approached at the PECARN sites using a probability sampling method provided by the Data Coordinating Center (DCC). For Study Two, the sample will be enriched for patients who present with psychiatric chief complaints, prioritizing these youth for recruitment over those who present with non-psychiatric chief complaints. The specific procedures used for screening and recruitment may differ at the Whiteriver site to accommodate for site-specific and cultural considerations.

1.3.1 Subject Accrual

Approximately 6,900 subjects will be enrolled for Study One. A subsample of approximately 3,000 of these subjects (43%) will also complete the computerized Implicit Association Test (IAT) during the initial study visit, and be contacted for follow-up assessments at 3 and 6 months. We will also conduct medical chart reviews for this subsample, which will include approximately: (a) 1,400 youths who present to the ED with high risk, defined by suicidal ideation with intent and/or plan, history of one or more suicide attempts, NSSI 5 or more times in the past 12 months, or homicidal ideation with current intent or plan; (b) 1,100 youths who present with either suicidal/homicidal ideation (without plan or intent) or two or more other well-established suicide risk factors; and (c) 500 youths at low/no risk for suicide. Additional subjects will be randomly selected for medical chart reviews so that the total number of subjects with chart review is approximately 4,000.

Approximately 4,000 subjects will be enrolled for Study Two, with an emphasis on enrolling youth who present with psychiatric (behavioral health) chief complaints to enrich for this group as much as possible compared with the enrollment of youth who present with other chief complaints.

1.3.2 Study Subject Accrual Duration

Accrual of subjects for Study One is anticipated to average 5 to 16 subjects per week at each site with approximately 129 per week across all sites. A subsample of these subjects will be followed by 3-month and 6-month outcome assessments. Development of the CAS algorithm will begin after the 3-month outcome data are finalized for data analyses.

Accrual of subjects for Study Two will prioritize enrollment of youth with a psychiatric chief complaint and is anticipated to average 5 to 16 subjects per week with approximately 129 per week across all sites.

2 Rationale and Background

Suicide is the 2nd leading cause of death among adolescents between the ages of 12-17 in the United States.[1] Moreover, national surveys in high schools show that the one-year point prevalence rates of suicide attempt and clinically significant suicidal ideation, are 7.8% and 15.8%, respectively.[2] Such suicidal thoughts and attempts are associated with personal and family suffering, psychiatric hospitalizations, psychosocial impairment, and risk for subsequent suicidal behavior, including suicide.[3–6] The U.S. National Strategy for Suicide Prevention[7] and the IOM[8] have identified suicide prevention as a national imperative.

2.1 Emergency Department as a Setting for Youth Suicide Risk Screening

Suicide risk screening in EDs has been shown to be acceptable to families, feasible, and effective at identifying previously unidentified youth at risk.[9–13] In a study of 1,590 ED patients, Claasen and Larkin[14] found that 12% presented with suicidal ideation and 2% with definite suicide plans. Chart reviews found that 81% of the patients planning suicide were undetected during their index visit. Common reasons for visiting the ED, such as trauma, interpersonal violence, or drug or alcohol abuse are also associated with suicidal risk, and in fact, a high proportion of youth identified as screening positive for suicide risk who present to EDs for non-psychiatric reasons have been previously unidentified and were not receiving mental health services.[9]

A strong case for suicide risk screening in EDs can be made because pediatric EDs have become a *de facto* mental health triage system. One-third of all adolescents visit the ED annually; the number of visits for suicide attempts and non-suicidal self-injury (NSSI) has doubled over the past 2 decades; and mental health visits overall to EDs have increased.[15, 16] Although ample data indicate that ED visits offer an excellent opportunity to identify behavioral health and psychiatric issues,[17] including risk for suicide,[11–13] few EDs screen for suicide, despite nearly 200,000 visits annually for suicidal thoughts or behavior.[18]

2.2 Challenges Inherent in Youth Suicide Risk Screening

2.2.1 Poor specificity of screening tools.

Despite the frequency with which adolescents present with attempted suicide, other self-inflicted injury, suicidal thoughts, or other suicide risk factors, screening and assessment instruments designed to identify the highest possible number of youth at risk (high

sensitivity) generally have high rates of false positives (low specificity). This protocol will attempt to improve the tools that can be used for suicide risk screening in the pediatric ED.

2.2.2 Youth often deny or conceal suicidal thoughts.

A major challenge in prediction of suicidal behavior is frequent motivation to deny or conceal thoughts of suicide for fear of being hospitalized or due to a strong desire to die. This may be particularly true for adolescent males for whom suicidal ideation is not as strong a predictor of suicide attempts as it is for females,[19, 20] despite the common use of suicidal ideation in screening.

Recent research suggests two potential approaches to this problem. Psychological scientists have developed behavioral (i.e., computer-based reaction-time) tests that can measure people's implicit cognition (i.e., their thoughts or mental associations that are automatic and outside conscious control). The Implicit Association Test (IAT) is an example, and will be assessed in this project. The second is adaptive testing, which develops algorithms for choosing subsets of items that will be most informative for suicidal risk, given a patient's answers to previous questions.

2.2.3 Heterogeneity of Risk Factors beyond Suicidal Ideation.

Risk factors for suicide attempts among adolescents can be categorized within demographic, clinical (e.g., suicide attempt history, psychiatric condition, mental status)[6] and family/social (e.g., history of physical or sexual abuse, bullying victimization)[21] domains.[22] Although certain primary risk factors, such as a history of suicide attempt, suicidal ideation, depression, alcohol or substance abuse, and aggression may be prevalent among adolescents who make suicide attempts,[23] none of these are necessary for a suicide attempt to occur.

2.2.4 Socio-demographic and Cultural Variation.

The substantial differences in suicide prevalence rates for subgroups of youth defined by socio-demographic factors have important implications for suicide prevention strategies, and indicate the importance of cultural considerations for prevention and screening. Specifically, the prevalence rate for suicide deaths is substantially higher for American Indian youth than for any other racial/ethnic subgroup of youth in the U.S.[24]A second striking demographic difference is that, across every racial/ethnic subgroup in the U.S., adolescent males are at substantially higher risk for suicide than adolescent females.[1] Thus, although suicidal ideation and suicide attempt prevalence rates are substantially higher

for adolescent girls than boys in the U.S.,[2] one screening challenge is to identify such risk in adolescent boys and in American Indian youth who may or may not present with a suicidal complaint. Personalized assessment through the use of a computerized adaptive screen (CAS), which will be studied in Study Two, has the potential to incorporate socio-cultural variations in risk factors.[25]

2.3 Advantages of CAS Over Static "One Version" Screens.

Mental health measurement, including suicide risk assessment, has been based primarily on subjective judgment and classical test theory. Typically, categorization of risk or disorder is determined by a total score, requiring that all respondents be administered the same items, and then allows measurement error to vary. This means that a classical approach to suicide risk screening will result in significant variation in measurement accuracy across respondents. While this is a significant problem for the determination of any construct, like depression, it is particularly problematic for suicide risk assessment because the contributors to risk are multiple and heterogeneous, and missing someone at high risk is potentially life-threatening.

Computerized adaptive screening (CAS) is an alternative to administration of a full battery of suicide risk measures or a brief, static suicide risk screen. With CAS, different youth may receive different scale items that are offered, conditional on their response to earlier administered items and are therefore targeted to their specific risk profile. Thus, CAS will yield a series of items that are personalized to an individual's risk profiles. The number and content of items vary among individuals in order to achieve the same precision of measurement in each. CAS is grounded in item response theory (IRT), in which an individual's initial item responses are used to determine a provisional estimate of their standing on the measured trait (e.g., risk of suicide attempt). This approach allows for an individualized selection of a subset of items that minimizes and standardizes measurement error for a given individual. This personalized approach, given the heterogeneity in suicide risk factors, makes it likely that CAS will outperform classical approaches to suicide risk screening.

3 Public Health Significance of Study

Youth frequently present to pediatric EDs with prominent suicidal risk, which in turn is a strong predictor of attempts and suicide. Therefore, rapid identification, triage, and referral of these youth for appropriate care could be life-saving. However, currently, the field lacks a rapid, sensitive and specific screen for suicidal risk that also provides guidance as to key modifiable risk factors. By identifying who is at highest risk, more restrictive

care could be more rationally allocated and utilized. By identifying key modifiable risk factors, the assessment could guide what type of treatment is needed and what are relevant treatment targets. The development and implementation of an adaptive questionnaire design could result in a brief, sensitive, specific instrument that is personalized and addresses the clinical needs of pediatric EDs and their patients.

4 Study Design and Data Collection

4.1 Study Design Overview

4.1.1 STUDY ONE

See Table 1 and 2 for Schedule of Events for Study One.

- Recruit a sample of approximately 6,900 youth, ages 12 to 17 years, presenting to EDs in the PECARN network and Whiteriver PHS Hospital (Apache sample) during randomly chosen screening shifts. ED-linked recruitment will be utilized at the Whiteriver site
- Administer a suicide risk self-report survey that includes history of suicide attempts, suicidal ideation, non-suicidal self-injury (NSSI), depression, aggression, alcohol and drug use, anxiety, insomnia, and other documented risk factors, and obtain parent reports of youth behavioral problems, adaptive functioning, and recent mental health treatment (recent hospital discharge and treatment adherence, if applicable).
- For an enriched subsample of approximately 3,000 youth (approximately 1,400 at high risk for a suicide attempt, defined by suicidal ideation with intent and/or plan, history of one or more suicide attempts, NSSI 5 or more times in the past 12 months, or homicidal ideation with current intent or plan; approximately 1,100 at risk with either suicidal/homicidal ideation (without plan or intent) or two or more other well-established suicide risk factors; approximately 500 at low risk), we will administer the Implicit Association Test (IAT), which examines implicit suicide-related cognitions.
- Follow-up the subsample of approximately 3,000 youth with interviews at 3 and 6 months, and obtain follow-up parent reports of mental health services utilization for those <18 years of age.
- Follow-up subsample of approximately 4,000 youth with medical chart reviews of return ED visits and hospitalizations.These youth will be comprised of the following

approximated groups: 1) 3,000 of the youth will be those included in the enriched subsample selected to complete the IAT, follow-up interviews, and parent reports, and 2) an additional 1,000 youth will be randomly selected from the 3,900 subjects remaining.

- Develop the CAS personalized screen using baseline, 3-month, and 6-month follow-up data.

4.1.2 STUDY TWO

See Table 3 and 4 for Schedule of Events for Study Two.

- Recruit a new sample of approximately 4,000 youth, ages 12 to 17, presenting to PECARN EDs and the Whiteriver PHS Hospital ED, with an emphasis on enrolling youth who present with a psychiatric complaint (vs. other chief complaints).

- Administer the CAS and ASQ screens, in addition to a brief survey of other suicide risk factors and the IAT, and obtain parent reports.

- Follow-up at 3 months (all youth) and at 6 months (the first 2,000 subjects enrolled) with youth interviews, follow-up parent reports (for subjects <18 yrs at 3 and 6 months), and medical chart reviews at 3 months (all youth) to examine the screens sensitivity and specificity for predicting suicide attempts.

4.2 Participant Screening and Enrollment

In order to avoid enrollment bias, the DCC biostatistician will create a randomized screening schedule for each site based on site research staff availability and local census patterns. The screening schedule will also take into account target enrollment milestones and the corresponding rate of enrollment that is required. ED-linked recruitment will be utilized at the Whiteriver site.

- **PECARN Sites**: Qualifying adolescents who meet eligibility criteria and their parent(s)/guardian(s) will be approached for participation sequentially, beginning at the times and on the days specified by the randomized schedule.

- **Whiteriver Site**: Qualifying adolescents who meet eligibility criteria and their parent(s)/guardian(s) will be identified and contacted for potential participation.

Table 1: Schedule of Events for Study ONE (All sites, excluding Whiteriver)

Study Procedures	**ED Visit**	**Month 3**	**Month 6**
Window		*(-2 weeks to +6 weeks)*	*(-2 weeks to +3 months)*
Screen for Eligibility	X		
Eligibility Checklist Review	X		
Consent/Parental Permission/Assent	X	X[4,5]	X[4,5]
Collect Contact Information	X		
Collect ED Visit Data	X		
Administer Youth Survey Measures	X	X[1,5]	X[1,5]
Administer Parent Survey Measures	X	X[1,5,6]	X[1,5,6]
Subject Selection for Additional Procedures	X		
Administer Youth Implicit Association Test (IAT)	X[1]		
Notify ED Clinical Team of Subjects Indicated for Suicide Risk, Physical Assault, and/or Sexual Abuse	X[2]		
Mental Health and/or Social Work Evaluation	X[2,7]		
Contact Crisis Hotline for Suicide Risk Subjects		X[3]	X[3]
Medical Record Review			X[1]
Adverse Event Assessment	X	X[1,5]	X[1,5]
Death Record and Missing Participant Search		X[1]	X[1]

1. Study procedure to be completed ONLY if youth has been selected to complete additional procedures.

2. Procedure to be completed ONLY if youth meets designated criteria for suicide risk, physical assault, and/or sexual abuse.

3. For youth who meet designated suicide risk criteria during follow-up, SRC staff will refer to Boys Town Hotline.

4. For subjects that reach 18 years of age prior to one of the follow-up assessments, adult consent from those youth will be obtained at the applicable time point.

5. Telephone follow-up will be conducted by the Survey Research Center (SRC) at the University of Michigan.

6. Parent survey measures will not be administered if youth participant has turned 18 years of age by the time of the 3- or 6-month follow-up assessment.

7. The mental health/social work evaluation(s) will be considered a standard of care procedure (not research related).

Table 2: Schedule of Events for Study ONE (Whiteriver ONLY)

Study Procedures	**Initial Study Visit**	**Month 3**	**Month 6**
Window	*(Within 1 week of ED Visit)*	*(-2 weeks to +6 weeks)*	*(-2 weeks to +3 months)*
Screen for Eligibility	X		
Eligibility Checklist Review	X		
Consent/Parental Permission/Assent	X	X[4,5]	X[4,5]
Collect Contact Information	X		
Collect ED Visit Data	X		
Administer Youth Survey Measures	X	X[1,5]	X[1,5]
Administer Parent Survey Measures	X	X[1,5,6]	X[1,5,6]
Subject Selection for Additional Procedures	X		
Administer Youth Implicit Association Test (IAT)	X[1]		
Notify Apache Surveillance System of Subjects Indicated for Suicide Risk, Physical Assault, and/or Sexual Abuse	X[2]		
Apache Surveillance System Evaluation	X[2,7]		
Contact Apache Surveillance System for Suicide Risk Subjects		X[3]	X[3]
Medical Record Review			X[1]
Adverse Event Assessment	X	X[1,5]	X[1,5]
Death Record and Missing Participant Search		X[1]	X[1]

1. Study procedure to be completed ONLY if youth has been selected to complete additional procedures.

2. Procedure to be completed ONLY if youth meets designated criteria for suicide risk, physical assault, and/or sexual abuse.

3. For youth who meet designated suicide risk criteria during follow-up Whiteriver study staff will refer to Apache Surveillance System.

4. For subjects that reach 18 years of age prior to one of the follow-up assessments, adult consent from those youth will be obtained at the applicable time point.

5. In-person or telephone follow-up will be conducted by the Whiteriver research staff for the Whiteriver PHS Hospital site.

6. Parent survey measures will not be administered if youth participant has turned 18 years of age by the time of the 3- or 6-month follow-up assessment.

7. The Apache Surveillance System evaluation will be considered a safety management procedure with appropriate follow-up measures (e.g. contact with Behavioral Health, Social Services, law enforcement, transfer to ED) determined on a patient-by-patient basis by this team.

Table 3: Schedule of Events for Study TWO (All Sites, excluding Whiteriver)

Study Procedures	**ED Visit**	**Month 3**	**Month 6**
Window		*(-2 weeks to +2 months)*	*(-2 weeks to +3 months)*
Screen for Eligibility	X		
Eligibility Checklist Review	X		
Consent/Parental Permission/Assent	X	X[3,4]	X[3,4]
Collect Contact Information	X		
Collect ED Visit Data	X		
Administer Youth Survey Measures	X	X[4]	X[4,7]
Administer Parent Survey Measures	X	X[4,5]	X[4,5,7]
Administer Youth Implicit Association Test (IAT)	X		
Notify ED Clinical Team of Subjects Indicated for Suicide Risk, Physical Assault, and/or Sexual Abuse	X[1]		
Mental Health and/or Social Work Evaluation	X[1,6]		
Contact Crisis Hotline for Suicide Risk Subjects		X[2]	X[2]
Medical Record Review	X	X[8]	
Adverse Event Assessment	X	X[4]	X[4]
Death Record and Missing Participant Search		X	X

1. Procedure to be completed ONLY if youth meets designated criteria for suicide risk, physical assault, and/or sexual abuse.

2. For youth who meet designated suicide risk criteria during follow-up SRC staff will refer to Boys Town Hotline.

3. For subjects that reach 18 years of age prior to the follow-up assessment, adult consent from those youth will be obtained.

4. Telephone follow-up will be conducted by the Survey Research Center (SRC) at the University of Michigan.

5. Parent survey measures will not be administered if youth participant has turned 18 years of age by the time of the follow-up assessment.

6. The mental health/social work evaluation(s) will be considered a standard of care procedure (not research related).

7. The 6-month youth and parent telephone follow-up will only be conducted with the first 2,000 subjects enrolled in Study 2.

8. All youth will have a medical record review completed for events through the 3-month time period.

Table 4: Schedule of Events for Study TWO (Whiteriver ONLY)

Study Procedures	**Initial Study Visit**	**Month 3**
Window	*(Within 1 week of ED visit)*	*(-2 weeks to +2 months)*
Screen for Eligibility	X	
Eligibility Checklist Review	X	
Consent/Parental Permission/Assent	X	X[3,4]
Collect Contact Information	X	
Collect ED Visit Data	X	
Administer Youth Survey Measures	X	X[4]
Administer Parent Survey Measures	X	X[4,5]
Administer Youth Implicit Association Test (IAT)	X	
Notify Apache Surveillance System of Subjects Indicated for Suicide Risk, Physical Assault, and/or Sexual Abuse	X[1]	
Apache Surveillance System Evaluation	X[1,6]	
Contact Apache Surveillance System for Suicide Risk Subjects		X[2]
Medical Record Review		X
Adverse Event Assessment	X	X[4]
Death Record and Missing Participant Search		X

1. Procedure to be completed ONLY if youth meets designated criteria for suicide risk, physical assault, and/or sexual abuse.

2. For youth who meet designated suicide risk criteria during follow-up Whiteriver study staff will refer to Apache Surveillance System.

3. For subjects that reach 18 years of age prior to the follow-up assessment, adult consent from those youth will be obtained.

4. In-person or telephone follow-up will be conducted by the Whiteriver research staff for the Whiteriver PHS Hospital site.

5. Parent survey measures will not be administered if youth participant has turned 18 years of age by the time of the follow-up assessment.

6. The Apache Surveillance System evaluation will be considered a safety management procedure with appropriate follow-up measures (e.g. contact with Behavioral Health, Social Services, law enforcement, transfer to ED) determined on a patient-by-patient basis by this team.

The DCC will prepare enrollment reports to monitor the screening and enrollment at each site to assess site performance and, if necessary, take corrective action.

For Study One, patients will be screened for eligibility and eligible patients and guardians will be contacted/approached for permission to participate in the study.

During screening windows in Study Two, there will be an emphasis on approaching and recruiting patients with a psychiatric complaint. Enrollment outside of pre-specified enrollment windows may also be allowed at some sites to assist with capture of patients with psychiatric chief complaints. This will be done in a systematic way to avoid enrollment bias.

- **PECARN Sites**: Recruitment and study procedures will occur when the patient and family are waiting to be seen by a clinician or during other waiting periods. Administration of the questionnaire can be interrupted or paused if medical care is needed, and resumed when the episode of medical care is completed.

- **Whiteriver Site**: Instead of immediate approach in the ED, recruitment will occur in-person or by phone after the patient has left the ED, within one week of the ED visit.

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 ED care and patient flow, and have been successfully utilized by the research team in multiple previous ED studies.[9, 10, 26–35]

During screening windows in Study Two, patients with psychiatric and non-psychiatric complaints will be recruited. Patients with psychiatric complaints will be prioritized for recruitment if needed to achieve an overall target ratio of approximately 3:2 (non-psychiatric to psychiatric patients). Enrollment outside of pre-specified enrollment windows may also be allowed at some sites to assist with capture of patients with psychiatric chief complaints. This oversampling will ensure an adequate representation of youth at elevated risk for suicide attempts, since a high proportion of youth with psychiatric complaints screen positive for suicidal risk.[9, 36] Youth participants will be identified via ED patient tracking systems for possible eligibility.

Study staff will contact/approach possibly eligible youth who were identified from the patient tracking systems. If parent/guardian written informed consent is obtained and the adolescent assents, the study staff will review instructions for completion of the CAS, the ASQ and the IAT behavioral test.

4.3 Suicide Risk Assessment

For Study One, this will consist of a youth self-report suicide risk survey, requiring approximately 30 minutes, and in Study Two requiring approximately 10-15 minutes. A parent self-report survey requiring approximately 5-10 minutes will also be completed for Study One and Study Two. All participating youth will be asked to complete the suicide risk survey, which will be comprised of approximately 100 self-report questions. These questions assess a wide array of suicide risk factors, with the greatest emphasis on those that hold the most promise for predicting acute or near term suicide risk. Questions assess lifetime history of suicide attempt, recent history of significant non-suicidal self-injury (NSSI), suicidal ideation (including intent, method, ruminative suicidal thoughts), and a wide range of other putative risk indicators for suicide attempts. These include alcohol/drug use, hopelessness, depression, anxiety, insomnia, agitation, and bullying victimization and perpetration, among others. The parent survey assesses demographics and family history of suicide in addition to youth behavioral problems, adaptive functioning and mental health services utilization. For the enriched sub-sample of approximately 3,000 youth, the survey also includes a behavioral test of implicit suicidal cognitions (IAT). See Table 5 and 6 for Adolescent Measures. See Table 7 and 8 for Parent Measures.

4.4 Patient Contact Procedures

For the PECARN sites, the SRC will receive notification regarding respondents selected for follow-up along with contact information. The respondent file will include contact information for multiple individuals who can assist with locating the respondent. SRC will attempt to send reminders (e.g. letter, postcard, e-mail) to respondents prior to their follow-up interview(s). SRC may perform additional tracking as needed. SRC may try multiple times to contact and interview each respondent, at 3 months and 6 months after screening/recruitment. In Study 2 the SRC will attempt to contact and interview at 3-months for all enrolled youth and a sub-set of approximately 2000 for the 6-month interview.

In the Whiteriver community, computer-assisted telephone interviews to collect outcome data are not feasible due to inconsistent home and cellular-telephone coverage in a rural context and a preference as indicated by the Community Advisory Board for in-person administration of assessments containing sensitive and personal information. Therefore in this sample, 3- and 6-month outcomes will be assessed via in-person or telephone interviews delivered by study staff. In addition, for the Whiteriver site, study staff may make use of telephone call and text reminders (due to frequent residence/address changes). For subjects who cannot be reached in this way, study staff may stop by residences of subjects to make sure they are at the same home location, verify phone numbers

Table 5: ADOLESCENT MEASURES STUDY ONE

	Time	**# of Items**
Ask Suicide-Screening Questions (ASQ)	ED/Initial	4
C-SSRS Screen	ED/Intial, 3&6m	7-21
Suicidal Ideation Characteristics	ED/Initial	0-5
C-SSRS: Behavior Scale (adapted)	ED/Initial, 3&6m	0-2
Homicidal Ideation	ED/Initial	1-2
Non-suicidal self-injury (NSSI)	ED/Initial, 3&6m	1-3
Patient Health Questionnaire-9	ED/Initial, 3&6m	9
Hopelessness (Mood and Feelings Questionnaire- 1 item)	ED/Intial, 3&6m	1
Alcohol Use Disorders Identification Test- Consumption	ED/Initial, 3&6m	3
Drug Use Scale	ED/Initial	5-8
Brief Agitation Measure	ED/Initial	3
SCARED-C (Short Version)	ED/Initial	5
Sleep Disturbance (PROMIS Sleep Disturbance Short Form 4a and Munich Chronotype Questionnaire - adapted)	ED/Initial	10
Impulsive Premeditated Aggression Scale-(Impulsive Aggression Subscale-adapted)	ED/Initial	1-5
UPPS Impulsivity Behavior Scale - Urgency	ED/Initial	4
Positive & Negative Affect Scale for Children-Positive Affect Subscale	ED/Initial	5
School Connectedness (Reduced)	ED/Initial	2
Social Connectedness (Reduced)	ED/Initial	2
Youth Risk Behavior Survey	ED/Initial	3
Family Connectedness Scale	ED/Initial	2
Peer Victimization/Perpetration	ED/Initial	4
DISC-IV Trauma Screen	ED/Initial	4-6
Sexual Identity, Behavior, and Attraction	ED/Initial	3
Life Experiences Survey	ED/Initial	4
Eating Attitudes Test (Bulimia)	ED/Initial	1
PHQ-10 (Adjustment item, adapted)	ED/Initial, 3&6m	1
Pubertal Development Scale	ED/Initial	3
Mental Health Service Utilization (presented to youth $\geq$ 18 yrs)	3&6m	4-8
Implicit Association Test (IAT)	ED/Initial	NA
Total # of Items		92-129

Table 6: ADOLESCENT MEASURES STUDY TWO

	Time	**# of Items**
CAS-Suicide Risk	ED/Initial	˜8-15
Ask Suicide-Screening Questions (ASQ)	ED/Initial	4
C-SSRS Hx Suicide Attempts (#) , NSSI Past 12 months (# times, # methods), Suicidal Ideation	ED/Initial, 3&6m	2-18
Patient Health Questionnaire-4	ED/Initial, 3&6m	4
Hopelessness	ED/Initial, 3&6m	1
Alcohol Use Disorders Identification Test - Consumption	ED/Initial, 3&6m	3
Drug Use Scale	ED/Initial, 3&6m	6
Youth Risk Behavior Survey: Fighting at school, weapon carrying	ED/Initial, 3&6m	1
Connectedness Scales from ED-STARS Study One: Parent-Family (2), Friends (2), School (2)	ED/Intial, 3&6m	6
Sexual Identity, Behavior, and Attraction	ED/Initial, 3&6m	4
Head Injury Assessment	ED/Initial	1-4
Positive & Negative Affect Scale for Children-Positive Affect Subscale	ED/Initial, 3&6m	3-5
Peer Victimization/Perpetration	ED/Initial	4
Implicit Association Test (IAT)	ED/Initial	NA
Total # of Items		˜45-74

Table 7: PARENT MEASURES STUDY ONE

	Time	**# of Items**
Demographics	ED/Initial	9
Mental Health Service Utilization	ED/Initial, 3&6m	4-8
Pediatric Symptom Checklist 17 (PSC-17) - Attention Subscale and Externalizing Subscale	ED/Initial	12
Family History Screen	ED/Initial	3-4
Patient Health Questionnaire-4	ED/Initial	4
PHQ-10 (Adjustment item, adapted)	ED/Initial	1
Total # of Items		33-38

Table 8: PARENT MEASURES STUDY TWO

	Time	**# of Items**
Demographics	ED/Initial	9
Mental Health Service Utilization	ED/Initial, 3&6m	4-8
Pediatric Symptom Checklist 17 (PSC-17) - Attention Subscale and Externalizing Subscale	ED/Initial	12
Family History Screen	ED/Initial	3-4
Patient Health Questionnaire-4	ED/Initial	4
PHQ-10 (Adjustment item, adapted)	ED/Initial	1
Total # of Items		33-38

and remind subjects of upcoming appointments. Study staff may either meet with youth and parent/guardian in their home, the local research office, or another private place of their choice, or they will contact the parent and youth by telephone.

4.5 3- and 6-Month Follow-up Assessments

The 3-month and 6-month assessments in Study Two will be identical to the 3- and 6-month assessments in Study One. For Study One, research staff will attempt to contact youth who complete the full screen survey and are selected for follow-up for 3-month and 6-month outcome assessments. Outcomes for youths recruited in PECARN-affiliated EDs will be assessed via computer-assisted telephone follow-up interviews conducted by the Institute for Social Research, Survey Research Center (SRC) at the University of Michigan. A short parent survey will also be conducted (if subject <18 years) during follow-up, updating contact information and assessing the youth's mental health service utilization. Because investigators at Johns Hopkins have found that phone interviews conducted by culturally unfamiliar researchers have low acceptance and feasibility at the Whiteriver site, follow-up interviews at this site will likely be conducted in-person by research staff who undergo training similar to the training of SRC staff. At the Whiteriver PHS Hospital, the research coordinators will attempt 3-month and 6-month outcome assessments through in-person follow-up meetings conducted either at youths' homes or another preferred private setting; however, where appropriate, follow-up can also be done via telephone at this site.

Since some participants will give responses indicating elevated and possibly even acute risk for suicide at the time of outcome assessment, the computer-assisted interview procedure will involve an initial attempt to contact the parent/guardian (if the subject is <18 years of age) followed by contact/interview with the youth participant. This will

ensure that a parent/guardian is available for minors if there is a situation of acute risk and parental involvement is indicated.

For subjects who reach the age of majority (18 years) after assenting in the ED but prior to the 3-month or 6-month follow-up interview, adult consent will be obtained from these former youth. All subjects will have given assent at the initial ED visit and will have familiarity with the study; however, this adult consent will be obtained at the phone and in-person follow-up interviews, when applicable, to ascertain continued interest in participation. A waiver of documentation of informed consent for those adults re-consented by telephone will be requested (see 7.2.1 on page 40).

4.6 Medical Record Reviews

Medical record reviews of ED visits and hospitalizations will be conducted for all youths recruited at the PECARN sites and the Whiteriver site who are identified for 3-month and 6-month follow-up. Site study staff will record medical chart data for the applicable time period following index ED visits for all participants.

- **Study One**: 6-month time period for all youth selected for the medical record review.
- **Study Two**: 3-month time period for all youth enrolled.

Study staff will document information about any return ED visits or hospitalizations. This will be done on an ongoing basis by each site for each subject. The incident rate of suicide attempts will include those derived by interview and record review and will be used for cost estimates. Because some subjects who initially assent at the age of 17 years will turn 18 years of age by the time the medical record review is to be performed, we will request a waiver of consent and authorization to collect this data (see 7.2.1 on page 40).

4.7 Search for Missing Participants and Death Record Reviews

Although the number of suicides and deaths due to other causes in this sample is likely to be low, such deaths may occur because suicidal youth are at increased risk for death due to suicide, homicide, or accidental death.[4]

There are various methods data regarding subject death could be obtained for this protocol. Information may be collected through the following methods:

1. The 3- or 6-month medical chart review,
2. The 3- or 6-month follow-up assessment with the subject and parent (subject <18 years), and/or

3. A search for a missing participant (e.g., search database, Whiteriver search strategies, National Death Index).

These methods are detailed further below.

Medical Chart Review

Study staff at each site, when completing the medical chart review, will record any available data regarding deaths.

3- and 6-Month Follow-up Assessments

The SRC (for PECARN sites) and Whiteriver research staff (Whiteriver site), when completing the follow-up assessments, will record any available data regarding deaths.

Search for Missing Participant

Survey Research Center: The SRC uses a search database to look for participants who do not respond to follow-up phone calls and this database will also document if death has occurred. If the database indicates that the participant has died, death records may be requested from the State in order to document time and cause of death. If unable to trace the participant through the search database, local papers may be searched for obituaries, and the relevant department at the State may be contacted to determine if there is a death certificate for this participant.

Whiteriver: For the Whiteriver site, study staff employ the following strategies, which have been approved by the tribe and local IRBs: 1) a study staff person has access to look up alternative contact information through the local Indian Health Service hospital; 2) study staff have experience looking for subjects at varying times of day and days of the week to ensure the highest likelihood of success in contacting them; and lastly (if needed), 3) study staff have been able to utilize their network of professional connections in the community (e.g., schools, local community mental health center, high-risk task force) to locate individuals without disclosing the details of study participation.

National Death Index: The National Death Index is another potential resource that can be used to trace individuals who may have died in other states. However, this Index is only current to about 2-3 years prior, and therefore will not be useful during the 3 year period, but may be used subsequently. We may clarify deaths by whether they were suicides,[37]or the result of other causes.

4.8 Participant Compensation

Subject compensation will be used at baseline and follow-up to encourage study participation and subject retention. Participants may be compensated for the time it takes to complete the baseline and when applicable, 3-month follow-up, and, 6-month follow-up assessments, as approved by each site's Institutional Review Board (IRB).

5 Data Analysis

5.1 Sample Size Calculations and Statistical Power

5.1.1 STUDY ONE

In Study One, the study will follow-up approximately 3,000 (43%) of the 6,900 youth, who are apportioned into 3 groups: (1) high risk, defined by suicidal ideation with intent and/or plan, history of one or more suicide attempts, NSSI 5 or more times in the past 12 months, or homicidal ideation with current intent or plan; (2) at risk (youths who present with either suicidal/homicidal ideation [without plan or intent] or two or more other well-established suicide risk factors; and (3) low risk. Assuming 75% retention, there will be 1,050 in the 'high risk' group, 825 in the 'at risk' group, and 375 in the 'low risk' group. Recent prospective studies have shown that in adolescents, the 12 month risk for an attempt in ideators is 29.2%, so for 6 months, the estimated risk is 14.6%[38] Since the risk is not linear, but is highest early in the follow-up period, 2/3 of these attempts will be assumed to occur in the first 3 months, so that the rate for ideators in 3 months will be 9.8%. If ideators had a plan, the risk is even higher, 53.8% in 12 months, 26.9% in 6 months, and with the same assumptions as above, 18% in 3 months. Since about 25% of ideators are planners, the assumptions for the risk for attempts are conservative. Consequently, for Study 1, the estimated event rates are:

Risk Group	N	# Retained	3 mo risk for attempt	# attempts	6 mo risk for attempt	# attempts
High	1,400	1,050	10%	105	15%	158
Moderate	1,100	825	3.3%	27	5%	41
Low	500	375	0.7%	3	1%	4

Power calculations for the CAS and IAT studies are predicated on the expected number of suicide attempts. Thus, in Study 1, 135 attempts out of 2,250 youth at 3 months would result in an effective cell size of 254 (2x2,115x135/2,250), allowing the detection of an effect size of d=.25, or f^2 =.13, with up to 20 covariates in a regression,[39]all assuming power =.80 with alpha set at .05.

In terms of the development and calibration of the CAS, enrollment will target 10 times the number of subjects to items to insure that the item parameters of the IRT models and the diagnostic classification algorithms (i.e. suicide behavior risk) will produce stable estimates.[40] The planned enrollment of 3,000 subjects will permit up to 100 items to be evaluated.

5.1.2 STUDY TWO

In Study 2, we will follow-up approximately 4000 and 2000 youth at 3 and 6 months, respectively. With 80% retention, we will retain approximately 3200 and 1600 for follow-up. Our sampling frame for Study 2 will preferentially enroll patients presenting with psychiatric complaints. Based on the distribution of subjects, we anticipate that we will be able to enrich our sample of youth who present with psychiatric complaints to approximately 40% of the full sample. Thus, we expect to have follow-up data for 1280 subjects with psychiatric complaints and 1920 without at 3 months. We will have follow-up data for 640 subjects with psychiatric complaints and 960 without at 6 months. Using information from previous studies, we have predicted that the risk of suicide at 3 months among patients presenting with psychiatric complaints is around 8%. At 6 months, the risk will be approximately 12%. These rates will provide approximately 102 and 77 suicide attempts among psychiatric subjects at 3 and 6 months, respectively. Among those who present to the ED for medical/surgical issues, the rate of suicide attempt will be around 1.5% at 3 months and 2.25% at 6 months, so that in that subgroup, the number of attempts in 3 months should be 29 and in 6 months 22. Therefore, the total number of attempts in Study 2 will be approximately 131 at 3 months and 99 at 6 months. The functional cell size for attempters vs. non-attempters for Study 2 is 2x3069x131/3200=251 at 3 months and 2x1501x99/1600=186 at 6 months. This will allow for the detection of an effect size at 3 months of d=.25, and an f2=.13 with 20 covariates in a regression, assuming power=.80 and alpha set at .05. At 6 months, these become d=.29 and f2=.16. In terms of power to detect differences in sensitivity and specificity between the CAS and the ASQ, we examined data for the 524 subjects (ages 10-21) who participated in the ASQ development study.[39]

Because the ASQ has not been validated prospectively for the prediction of suicide attempt, two studies that examined the validity of the SIQ/SIQ-JR (criterion standard in ASQ study) for predicting future suicide attempt were used to inform our power calculations. In both studies, sensitivity was approximately 0.80, whereas specificity was 86% in one, and 41% in another.[41, 42] Using a two-sided McNemar's Test and with numbers of suicide attempts of 131 and 99, we will have power of at least 80% to detect a 0.09-0.11 difference in sensitivity between the CAS-based algorithm and the ASQ at 3

months and a 0.12-0.14 difference at 6 months. More generally, in terms of area under the curve (AUC) for a comparison of ROC curves, AUCs have been reported in the range of 0.6 to 0.7 for suicide attempt screening (AUC=0.57, 0.67, 0.72).[41, 43, 44] Based on the proposed sample size and prevalence rate, the study will have 80% power to detect a difference in AUC of 0.60 vs. 0.69 with 100 events and 0.70 vs. 0.79 with 92 events. Even with 99 attempts at 6 months, we will have around 80% power to detect such differences.

Power to predict a suicide attempt using the IAT. The S-IAT was tested in a sample of 89 adolescents (38 non-suicidal, 37 suicidal ideators, 14 recent suicide attempters), and found to be able to discriminate ideators, attempters, and non-attempters (d's .78-1.28), and more importantly, to predict attempts in the next 6 months (d=.52).[45] Effect sizes from this and other studies for predicting suicidal ideation and suicide attempt after adjusting for demographic and clinical risk factors are .44 and 1.0, respectively. The functional cell size for Study 2 is 251 at 3-month follow-up, which will allow for the detection of differences between groups of d=.25. The functional cell size is 186 at 6-month follow-up, which will allow for the detection of differences between groups of d = .29.[45, 46]

5.2 Computerized Adaptive Screening

This project will use two complementary approaches to computerized adaptive screening (CAS). First, in order to generate an algorithm that most efficiently identifies those youth most likely to make a suicide attempt in the next 3 or 6 months, Computerized Adaptive Diagnosis (CAD) will be used. Second, Computerized Adaptive Testing (CAT) will be used to generate a distribution of risk, since a second goal is to develop a triage model to allocate youth into imminent suicidal risk, need for mental health referral but not at imminent risk, and low risk. CAT is criterion free and uses IRT to estimate a person's standing on an underlying latent variable of interest based on the inter-relationships among the symptom items. This latent variable could be suicide risk based on a large number of relevant symptom-items and risk factors, and thresholds on this underlying continuum can be used to classify individuals into categories of high, moderate, and low risk. Gibbons et al.[40] have shown how CAT can be used to develop a dimensional measure of depression severity and to derive thresholds that correspond to none, mild, moderate, and severe depression. By contrast, CAD requires an external criterion and yields a binary prediction and associated level of confidence. Use of these two complementary approaches will yield a binary prediction of suicidal risk over a determined period of time with CAD, and allocation of individuals to levels of risk (e.g., high, moderate, and low) with CAT.

5.2.1 The Bifactor IRT Model

Most applications of IRT are based on unidimensional models that assume that all of the association between the items is explained by a single primary latent dimension or factor (e.g., mathematical ability). However, mental health constructs are inherently multidimensional. For example, in the area of depression, items may be sampled from the mood, cognition, behavior, and somatic sub-domains, which produce residual associations between items within the sub-domains that are not accounted for by the primary dimension. Attempts to fit such data to a traditional unidimensional IRT model require us to discard the majority of candidate items to achieve a reasonable fit of the model to the data. By contrast, the bifactor IRT model[47, 48] permits each item to tap the primary dimension of interest (e.g. depression) and only one of several sub-domains (e.g., somatic complaints), thereby accommodating the residual dependence and allowing for the retention of the majority of the items in the final model. The bifactor model of Gibbons and Hedeker was the first example of a confirmatory item factor analysis model, and they showed that it is computationally tractable regardless of the number of dimensions, in stark contrast to exploratory item factor analytic models. Furthermore the estimated bifactor loadings are rotationally invariant, greatly simplifying interpretability of the model estimates. The project investigators have developed the underlying statistical theory and methodology necessary to apply multidimensional CAT to the measurement of mental health constructs.[40]

5.2.2 Screening for Prediction of Suicide Attempt

The project methods are based on representing the classification of study participants as a decision tree. Decision trees[49–51] represent a model in terms of a flow chart. Decisions are made by traversing the tree starting from the top node. At each node in the tree, a participant is asked to respond to a particular item. The participant progresses down the tree to the node to the left if his or her response is less than the cut-off value for the node and to the right, otherwise. The bottom node of the tree reports a classification for the participant (0 = non-suicidal, and 1=suicidal). Decision trees are appealing in this context since they allow the set of items presented to adapt to the responses already provided - going left at a node may result in a very different set of items being presented as compared to going right. This has the potential to considerably shorten the length of the instrument.

Despite their appeal, decision trees have frequently suffered from poor performance because algorithms used to build trees can exhibit sensitivity to small changes in the derivation data sets. Instead, ensemble models constructed of averages of hundreds of decision trees have received considerable attention in statistics and machine learn-

ing.[49, 52–54]These models provide significant improvements in predictive performance as compared to individual trees. However, averaging hundreds of trees destroys the adaptive testing structure that makes them useful for medical questionnaires.

In order to obtain both the advantages of individual trees and the accuracy of ensemble models, this project will use a combined approach. The derivation data (from Study One) will be fit using random forests[49] because this ensemble modeling approach requires minimal human intervention and random forests have historically exhibited good performance across a wide range of domains.[49, 55] Using the results of the random forests models, a very large bootstrap data set will be created, representing the distribution of the items in the original data set. A single tree will be estimated from the bootstrap, reducing the sensitivity of the derived tree to small perturbations in the original data.

All estimation will be performed in the R statistical programming language using the RandomForest module.[56] Trees of multiple depths (e.g. depth 6 and 11 items each) will be used in the analysis. The optimal tree will be assessed with ten-fold cross-validation. External validation will be performed with an independent confirmatory sample (subjects enrolled in Study Two).

5.3 Specific Aim Analyses

Specific Aim 1. To develop an optimal suicide risk screen for youth presenting to the emergency department (ED). We will develop a personalized, computerized adaptive screen (CAS) and compare its psychometric properties (e.g., sensitivity, specificity, positive and negative predictive value) for predicting one or more suicide attempts to those of the Ask Suicide-Screening Questions (ASQ).

Overall sensitivity, specificity, PPV, NPV, likelihood ratios (LRs) and 95% confidence intervals will be computed for each screening method. Statistical significance will be based on comparison of AUC for the ROC curves for the two methods.

Specific Aim 2. To develop and validate a parsimonious CAS algorithm for risk stratification of youth to "high risk for suicide attempt" (high probability), "at risk" (need for mental health referral but no high risk) and "low risk" (low probability, no need for mental health referral) groups.

The specific criteria for risk stratification (threshold decisions) will be developed statistically, with high, medium, and low risk categories. The CAS is a dimensional measure that will give high risk (i.e., defined by an attempt within the 3-month follow-up period), moderate risk (defined by scores above screen cutpoints on one or more suicide

risk factors), or low risk (defined by no suicide attempt and low level of suicide risk). The CAS can be designed to provide an algorithm to classify youth into risk categories.

Specific Aim 3. To validate the CAS personalized suicide risk screen prospectively, examining its sensitivity and specificity for the 3-month and 6-month prediction of suicide attempts.

The CAS using both CAT and CAD will be developed in the calibration sample (Study One). The CAT and CAD versions of the CAS will then be independently validated in the confirmatory sample (Study Two) by estimating sensitivity, specificity, PPV, NPV and associated confidence intervals. Using this methodology, Gibbons et.al.[57] found sensitivity of 0.95 and specificity of 0.87 for a clinician-based DSM diagnosis of MDD using an average of only 4 items drawn from a bank of 100 items. The CAT and CAD versions will be assessed by comparing AUCs for the ROC curves for the two CAS measures (the screen and the risk stratification algorithm based on CAT and CAD) and the ASQ comparator-screening instrument.

Specific Aim 4. To determine if the IAT adds incrementally to the prediction of suicide attempts above and beyond CAS and ASQ scores.

The relevant metric derived from the IAT is the "D score," which is a measure of the mental association a person holds between the concepts of "death" and "me." A *D* score is calculated for each youth by subtracting the average response latency of the "death=not me" test block from the average response latency of the "death=me" test block and dividing by the standard deviation of response latency for all trials. Thus, positive *D* scores represent relatively faster responding (i.e., stronger associations) when "death" and "me" are paired, whereas negative *D* scores represent relatively faster responding when "life" and "me" are paired.

By comparing AUC between the screeners with and without the IAT, analyses will determine the extent to which the IAT adds to the predictive accuracy/validity of the CAS (and the ASQ), using hierarchical logistic regression and Cox regression (to examine prediction of time to suicide attempt as well). This will be tested in the calibration sample and then confirmed in the validation sample.

5.4 Exploratory Analyses

Exploratory analyses will be conducted to: (1) examine the performance of the CAS and the ASQ in important demographic or other subgroups (e.g., ethnicity, gender, same-sex

attraction, chief complaint); (2) determine if there are significant subgroups for whom the IAT significantly improves prediction over the CAS and/or ASQ in the prediction of suicide attempts; and (3) estimate the cost and cost savings associated with screen strategies. Logistic regression models will include the CAS or ASQ prediction, main effects of important demographic or other factors, factor by ASQ, and factor by CAS interactions as predictors, and suicide attempt within 6 months (calibration sample) and 3 months (validation sample) as the outcome. Tests of interactions will be used to determine the extent to which these specific factors of interest moderate the performance of the CAS and/or ASQ.

Economic analyses will include decision analysis using a Markov model to compare the costs and potential cost savings of screening for suicide risk compared with no screening. The Markov model will be used to simulate the potential cost utility associated with screening.[58] The model will estimate the gain in quality adjusted life years (QALYs) due to prevention of suicide attempts through screening and triage, as well as the associated costs.

6 Data Management

6.1 Johns Hopkins University

The PECARN Data Coordinating Center (DCC) will be the primary site for data management and data analyses. However, as mandated by the Apache tribal nation, Johns Hopkins will perform data management on their behalf. All data (screening and outcome) from Whiteriver (primarily Apache) will be collected on a portable computer device using a text-to-voice software to address three important cultural considerations: 1) Past research with American Indian youth indicate lower literacy levels than the general population. Text-to-voice software enables private, audio-assisted administration of assessment questions (through use of headphones) to participants with low literacy. 2) Through text-to-voice software, assessment questions can be tailored to reflect language preference and relevance for the American Indian population based on feedback from the Community Advisory Board and pilot testing with youth. 3) Finally, use of text-to-voice software ensures the Apache retain ownership and control of their unique data set in this protocol, as is customary when collecting data in tribal communities.

Data collected from Whiteriver will be transferred from the portable computer device to Johns Hopkins data management in a secure and encrypted manner. De-identified data (data that does not include information such as name, date of birth, etc.) will be transferred to the DCC at the University of Utah using secure electronic transfer.

During the last part of the grant period, Johns Hopkins investigators and Apache

research staff will analyze and present the study data to the Apache Community Advisory Board for input and interpretation. Hopkins investigators will also cooperate with study investigators and the DCC statistical investigators on cross-site data interpretation, and dissemination of findings via manuscripts and presentations to key stakeholder groups, including tribal leaders and Indian Health Service leadership.

The separate Apache Community Advisory Board (CAB) will meet throughout the study to review progress towards objectives, including recruitment numbers, basic demographic information on participants, and any feedback from community members pertinent to acceptability.

6.2 Survey Research Center (SRC) at the Institute for Social Research, University of Michigan

The Survey Research Center (SRC) at the Institute for Social Research, University of Michigan, will implement all computer-assisted interview (CAI) telephone-based outcome assessments for youth participants from PECARN affiliated sites. The SRC's centralized telephone facility, or Survey Services Laboratory (SSL), is equipped with a networked system of desktop computers and VOIP-enabled telephones.

For quality assurance on telephone surveys, the study will use a combination of live monitoring by supervisors and the review of digital recording – both audio and video (from the interviewer's phone and computer) files are stored on a secure network location. The files are stored on dedicated servers behind fire walls, with no direct linkage to any other files and are used solely for quality assurance purposes to evaluate the performance of the interviewers. These digital recordings can also be made available to approved members of the research team throughout data collection. In addition to the use of monitoring and review of digital recordings, the SRC conducts regular data reviews to check for quality problems.

Data collected from the SRC will be transferred to the DCC at the University of Utah using secure electronic transfer.

Files will be destroyed per SRC protocol either 3 months after the end of the project or after SRC involvement in the data collection component is complete (whichever comes first).

6.3 PECARN Data Coordinating Center (Utah)

In addition to locally secured, identifiable information, partially identifiable information for all sites will be maintained at the PECARN Data Coordinating Center, located at the University of Utah in Salt Lake City, Utah. The Data Coordinating Center

has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, cooling system and separate air filtering. The server facility is locked separately from the remainder of the Data Coordinating Center and access to the building is monitored by security personnel year round. The Data Coordinating Center coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the Data Coordinating Center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University.

Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 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 Data Coordinating Center machines is only available while physically located inside the Data Coordinating Center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against the servers, and IT staff are notified of intrusion alerts.

Production servers running mission critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. Storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly during the week. Incremental backups also are performed nightly with full system backups occurring every week. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken to an off-site commercial storage facility. Security is maintained with Windows 2008 user/group domain-level security.

Users are required to change their passwords every 90 days, and workstations time out after 5 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.

6.4 DCC Electronic Data Capture Systems

Under the direction of the DCC PI and biostatistician, and in collaboration with study investigators, the DCC will be involved with the development of electronic data capture systems to collect information on screening and enrollment, survey responses, safety measures, and medical chart review. The DCC uses a web-based interface designed specifically

for clinical trials and observational studies. The DCC has developed a sophisticated software system for managing data discrepancy queries. This Query Management System allows for data checks on individual data fields (e.g., for missing or out-of-range data) in addition to the validation of data between different forms. This helps ensure that data will be complete and valid.

6.5 Data Confidentiality

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 Data Coordinating Center are fully committed to the security and confidentiality of all data collected for PECARN studies. All Data Coordinating Center 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 Data Coordinating Center that relate to maintenance of passwords, information system security, and data confidentiality.

6.6 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 subject 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 may be conducted to review patient safety and to assure regulatory compliance and may be separate or combined with regular PI site visits described above, depending on the issues. The site monitor will provide sites with a written report and sites will be required to correct any deficiencies.

6.7 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating

Center, 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, Food and Drug Administration, and the Institutional Review Board (IRB) for each study site.

6.8 Data Collection

Information about recruitment efforts will be collected on eligible youth, ages 12-17 years who present during recruitment windows. Data collected may include variables such as eligibility criteria and consent/assent indicators as well as all other applicable data collected for this study. Participating youth will complete surveys through the secure web-based survey program. These data for PECARN sites will be housed and managed at the DCC and SRC where applicable, and at Johns Hopkins for the Whiteriver site.

7 Protection of Human Subjects

7.1 Institutional Review Board (IRB) Approval

Institutional Review Board (IRB) approval is required at all participating clinical sites as well as the Data Coordinating Center at the University of Utah. The DCC will track annual IRB evaluations at all sites. If a site allows its IRB approval to lapse, the site will not be permitted to enroll additional subjects nor perform follow-up procedures until IRB approval is documented at the DCC. Lapses that occur at sites may be reported, as a performance measure, to the study investigators, the NIMH Project Officer, and in interim DSMB reports.

7.2 Permission, Assent, and Consent Requirements

Parental permission and patient assent are required for a patient to participate in this study. In addition, parents must also consent to their own participation for a patient to participate in this study. Subjects will be informed of the purpose (i.e. screening for suicide risk) and procedures of the study. For subjects who reach the age of 18 prior to the three or six-month follow-up, re-consent will be obtained by telephone for subjects recruited at PECARN sites and in person or by telephone for subjects recruited at the Whiteriver site.

Participating sites are responsible for conducting adequate consent procedures and processes with each parent/guardian and youth. All participants should receive a verbal (or other appropriate means) explanation in terms suited to their comprehension on

the purposes, procedures, and potential risks of the study and their right as research participants. Participants should have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing.

7.2.1 Waivers Requested

1. **Waiver of Authorization:** A waiver of authorization will be requested in order to be able to pre-screen/establish eligibility for participants prior to approaching, consenting, and enrolling a patient.

2. **Waiver of Consent and Authorization:** Because some subjects who initially assent at the age of 17 years will turn 18 years of age before the medical record review occurs, a waiver of consent and authorization will be requested to collect this data for this group of participants.

3. **Waiver of Documentation of Consent:** This waiver will be requested for those subjects selected for telephone follow-up, who reach the age of majority (18 years), prior to the 3-month or 6-month telephone follow-up interview. Adult re-consent will be obtained over the phone to confirm the subject's continued interest in participating in the research study. Verification that the re-consent process occurred and the subject's verbal agreement will be documented by the research personnel.

7.3 Alternatives to Participation

Subjects do not receive any treatment in this study or forego any treatment in order to participate in this study. The alternative, therefore, is not to participate.

7.4 Potential Risks & Discomforts, and Anticipated Benefits

The potential primary risks of this study are emotional discomfort of the subject from completing the study questionnaires as well as loss of privacy and breach of confidentiality of the subject. With concern to emotional discomfort, completion of the surveys is voluntary and subjects will be told that they do not have to complete any questions that make them feel uncomfortable. Regarding loss/breach of privacy and confidentiality, all applicable parties (e.g. sites, DCC, SRC) will be responsible for ensuring that appropriate data security procedures are in place.

There are no likely benefits anticipated from participation in this study; however, there is potential benefit to others because of the knowledge that may be gained from this research.

7.5 Immediate Clinical Safety Assurance

This study assesses suicide risk in patients who present in the ED setting, and does follow-up assessments at three and six months. These assessment procedures may indicate that the participating subject is at an elevated risk of an impending suicidal event, and information from the research study needs to be conveyed to a clinical team so that the needs of the patient (as opposed to the subject) can be immediately met. The procedures differ in the initial ED setting from the subsequent follow-up assessments.

7.5.1 Emergency Department Clinical Procedures

Although ED-STARS is not an intervention trial, the screening and evaluation procedures of the study will identify participants who meet designated criteria for suicide risk, physical assault, and/or sexual abuse (based on level operationally defined in risk management protocol). Subsequently, for these subjects, the study procedures are outlined below:

- **PECARN Sites**: To notify the ED clinician with the expectation that a mental health and/or social work evaluation will be obtained for the youth, as per usual care.

  As part of the study procedures for these youth, study staff will document that: (1) the clinical team was notified of these concerns; (2) a mental health and/or social work evaluation took place; and whether (3) a suicide risk management plan was developed; and (4) a mental health referral was made.

  > *Note: It will be defined as a protocol violation if the clinical team is not notified and/or if a mental health and/or social work evaluation does not take place.*

- **Whiteriver site**: To notify the Apache Surveillance System with the expectation that they will follow-up to evaluate the youth and determine severity of risk and connect the youth with appropriate services.

  As part of the study procedures for these youth, study staff will document that: (1) the Apache Surveillance System was notified of these concerns; (2) an evaluation by the Apache Surveillance System took place; and whether (3) a suicide risk management plan was developed; and (4) a mental health referral was made.

  > *Note: It will be defined as a protocol violation if the Apache Surveillance System is not notified and/or if an evaluation by this team does not take place.*

These data will be reported on an interim basis to the Data Safety Monitoring Board, described later in this protocol. The absence of appropriate notification and evaluation documentation for applicable subjects will be communicated with a study principal investigator, as soon as it is noted by the DCC, who will follow-up directly with the investigator at the clinical site to determine the appropriate site follow-up to assure that such a lapse does not recur.

7.5.2 Follow-Up Clinical Procedures

- **Telephone Follow-Up Clinical Procedures** The status of selected participants during the 3- and 6-month follow-ups will be assessed by computer-assisted telephone interview by the Survey Research Center (SRC) at the University of Michigan. Although the experienced interviewers employed by the SRC will be trained specifically for this study and closely supervised, they are not clinicians. The primary outcomes assessed during the telephone follow-up interviews will be suicidal ideation, suicide attempts since the previous study assessment, non-suicidal self-injury (NSSI) and mental health service utilization. The interviewer will notify the youth's parent or guardian to confirm if they are available by telephone prior to contacting the youth for follow-up, in case there are safety concerns. The SRC interviewers are required to follow a safety protocol if the youth expresses suicidal ideation with an intent or plan, or has made a recent suicide attempt during the past 3 months or since the last study assessment. The SRC script will detail the specific triggers that lead to implementation of the safety protocol. The current protocol is to contact the youth's parent to notify him or her of the child's status and to connect the youth with the Boys Town National Hotline, which has an established approach to evaluating suicide risk and managing suicidal crises, if the latter is warranted. The interviewer will attempt (good faith effort) to contact the consenting parent or another legal guardian if the youth triggers positive for suicide risk at the time of the follow-up call, and should the consenting parent or other legal guardian be unavailable, due to safety considerations, we will share/disclose the youth's elevated suicide risk status with any adult at youth's home. If deemed necessary or beneficial by the Boys Town National Hotline counselor, the counselor will conference in the parent or guardian. Because linkage to the Boys Town National Hotline may occur, the SRC follow-up interviewers' script and instructions will include specific steps on appropriate notification to the Boys Town National Hotline, linkage of the family/subject with that resource, and additional follow-up procedures that may be needed.

  The SRC has previous experience with safety management protocols. Information

about SAEs as well as protocol violations will be provided to the PECARN DCC within 24 business hours of becoming aware of their occurrence, as applicable. Information about protocol violations wherein the SRC staff fail to contact Boys Town National Hotline regarding a high risk subject will be provided to both the PECARN DCC and the Safety Monitor (due to risk management issue) within 24 hours of occurrence. The electronic data capture system will include forms to allow documentation that a referral to a crisis line took place for subjects who are identified at risk.

- **In-Person Follow Up Clinical Procedures** The status of participants at 3 and 6 months after being seen in the ED for the Whiteriver site will be assessed in person or by telephone interview by Whiteriver study staff. Although the experienced interviewers employed by Johns Hopkins will be trained specifically for this study and closely supervised, they are not clinicians. The primary outcomes assessed during the in-person or telephone follow-up interviews will be suicidal ideation, suicide attempts since the previous study assessment, non-suicidal self-injury (NSSI) and mental health service utilization. The Whiteriver study staff interviewers are required to follow a tribally mandated protocol if the youth reports any suicidal ideation, has made a suicide attempt since the last study assessment, or has engaged in NSSI since the last study assessment, per the Apache Suicide and Self-Injury Surveillance System.[59] The protocol is to contact the youth's parent to notify him or her of the child's status and to connect the youth and parent (or subject only if 18 years of age) with the surveillance system, which has an established approach to evaluating suicide risk and managing suicidal crises, if the latter is warranted. Because linkage to the surveillance system may occur, interviewers' script and instructions will include specific steps on appropriate notification to the surveillance system, linkage of the family/subject with that resource, and additional follow-up procedures that may be needed.

  Information about SAEs as well as protocol violations will be provided to the PECARN DCC within 24 business hours of becoming aware of their occurrence, as applicable. Information about protocol violations wherein a subject meets high risk criteria and study staff fail to contact the surveillance system will be provided to both the PECARN DCC and the Safety Monitor (due to risk management issue) within 24 hours of occurrence. The electronic data capture system will include forms to allow documentation that a referral to the surveillance system took place for subjects who are identified at risk.

7.6 Adverse Event Definitions and Monitoring

Adverse events (AE) are defined as worsening of existing conditions or the new occurrence of an adverse condition occurring during a study. Serious adverse events (SAEs) are defined in Federal regulations. For this study, subjects will be monitored for AEs and SAEs as described below:

STUDY 1:

- **For subjects not selected for follow-up assessment and medical record review:** from the time of parental permission and patient assent to participate in the study through:
  PECARN Sites ED discharge.
  Whiteriver Site end of Initial Visit.
- **For subjects selected for medical record review only:** from the time of parental permission and patient assent to participate in the study through the 6-month record review.
- **For subjects selected for follow-up assessment and medical record review:** from the time of parental permission and patient assent to participate in the study through the 6-month record review or through the end of the 6-month follow-up assessment (whichever occurs last).

STUDY 2:

- **For ALL subjects NOT selected for the 6-month follow-up:** from the time of parental permission and patient assent to participate in the study through the 3-month record review or through the end of the 3-month follow-up assessment (whichever occurs last).
- **For subjects selected for the 6-month follow-up:** from the time of parental permission and patient assent to participate in the study through the 6-month follow-up assessment.

The following adverse and serious events will be reported for this study:

Adverse Events

- Distress during assessments
- Breach of confidentiality (access of confidential information by a non-authorized person)
- Evidence of coercion to participants

- Suicidal ideation with intent, method, and/or plan (identified during a follow-up interview assessment) resulting in referral to a crisis resource
- Non-suicidal self-injury (NSSI)

Serious Adverse Events

- Death for any reason
- Suicide attempt (defined as an action taken with any level of intent to die, as stated by the patient or noted in the medical record)
- Inpatient hospitalization, suicide- or potentially suicide-related
  - Suicidal ideation
  - Non-suicidal self-injury (NSSI)
  - Other mental health event (e.g., depression, homicidal ideation, anxiety)
- Emergency department (ED) visit, suicide- or potentially suicide related
  - Suicidal ideation
  - Non-suicidal self-injury (NSSI)
  - Other mental health event (e.g., depression, homicidal ideation, anxiety)

Expectedness: Because of the nature of the population under study, all AEs and SAEs listed in the table are considered expected. *Relatedness*: Since this study does not have any intervention, AEs and SAEs listed in the table are unlikely to be related to study procedures. For these reasons, expectedness and relatedness will not be collected for this study.

Supplementary information (an SAE report) will be required by the PECARN Data Coordinating Center staff for serious adverse events. This information will include brief narrative description of the event, which will be reviewed by the Medical Monitor (PI of the DCC, Dr. Dean, or his physician delegate).

All serious adverse events (SAE) must be reported to the PECARN DCC within one business day of the research team becoming aware of the event. Full SAE reports must be submitted to the DCC within the subsequent 72 hours. The Medical Monitor (PI of the DCC, Dr. Dean, or his physician delegate) will review all SAEs within 1 business day of receipt by the DCC. If the Medical Monitor has a concern with any SAE, in terms of potential ongoing risk issue, he will notify the project's Safety Monitor for follow-up. In addition, all SAEs will be reported to the DSMB in the tri-annual data reports, with the exception to subjects deaths or SAEs identified by the medical monitor as raising a concern of a potential ongoing risk issue.

7.7 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP), in general, to include any incident, experience, or outcome that meets all 3 of the

following criteria:

1. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; **AND**

2. **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research) or if the event or problem probably or definitely affects the safety, rights, and welfare of current participants; **AND**

3. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

The Site Investigator will report unanticipated problems to the DCC within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the NIMH representatives in an expedited manner (within 24 hours). In accordance with local IRB requirements, the Site Investigator may be required to report such unanticipated problems to the IRB in addition to notifying the DCC.

In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and Program Officer staff cannot be reached expeditiously, the DCC will notify the study investigators and all Site Investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the Program Officer and Principal Investigators after discussion with the DSMB. After notification of the Program Officer, and the DSMB chairperson, of unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigators and all clinical investigators, who will be instructed to report this to their local IRB.

7.8 Data Safety Monitoring Board (DSMB) Reporting

The DSMB will be appointed by the NIMH, and will approve the final version of this protocol as well as all subsequent protocol amendments and corresponding study materials

(e.g., study consent forms, study procedures) that may be applicable. The DSMB will also have a charter for operation. The logistics and frequency of the DSMB meetings will be determined by NIMH and will be coordinated with the PECARN Data Coordinating Center in accordance with NIMH requirements. Details of DSMB operation are defined in the NIMH DSMB charter.

The DCC biostatistician will oversee preparation of DSMB reports containing data on safety and adverse events, study outcome events, and result summarization. Reports will include summary information relating to screening and enrollment (overall and by site), reasons for excluding patients, and baseline characteristics of enrolled subjects. Protocol violations as well as requested data quality monitoring information will be reported to the DSMB, as applicable. Adverse events will be coded using the MedDRA coding dictionary, and adverse event summaries will be presented by System Organ Class and Preferred Terms. All serious adverse events will be presented together with details about the events. The DSMB report will also include information concerning the acute disposition of patients who were assessed at high risk in the ED or on follow up, and required intervention.

Since this is an uncontrolled non-interventional study, the traditional approach of presenting data by study arm is not applicable. There are two planned approaches to DSMB reporting to elucidate whether participation in the study is endangering participants. First, the overall frequency of study outcome events (suicidal events or attempts) will be compared to the previously published frequency estimates for similar populations, stratified according to the risk categorization from the ED screening procedures. This is an inexact comparison, for sure, because the underlying populations for validating the screening tools were not adolescents presenting in the pediatric ED setting. However, very large differences from the expected frequency may indicate harm (or benefit) from participating in the study. Second, the temporal relationship of study outcome events with the ED evaluation and the subsequent follow up assessments will be measured. It is not reasonable to assume that this temporal relationship should be random, because the initial presentation of patients (particularly in Study Two) may bias toward higher risk of a suicidal event. For example, a patient presenting with mental illness may be at higher risk of suicidal ideation or an impending attempt - this higher risk may have led the individual patient to decide to go to the ED for intervention.

8 Study Training and Monitoring

8.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each Clinical Center investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study investigators (Drs. King, Grupp-Phelan, Brent), will be the main contact for study questions.

8.2 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous PECARN studies, and we will utilize this process to ensure excellent quality data in the proposed study. Our site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Site monitors must be provided with full access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

8.2.1 Site Monitoring Plan

A supplemental study-specific monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review and a follow-up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found. Remote site monitoring schedules will be determined by the Data Coordinating Center in coordination with the study principal investigator.

8.2.2 Clinical Site Monitoring

Site monitoring visits may be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits may take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow-up on any deficiencies

8.2.3 Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the Clinical Center and consultations with the Clinical Center investigator and/or research coordinator to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record, patient study file, regulatory documentation, or other source documents to the Data Coordinating Center staff, who review those materials against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring the documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

9 Regulatory Issues

9.1 Health Insurance Portability and Accountability Act

The abstracted data will include limited identifiers as defined by the Health Insurance Portability and Accountability Act, and specific contact information will be provided to research staff conducting follow-up with parents. Abstracted data will be retained and archived at the Data Coordinating Center in accordance with record retention requirements of the NIH. Contact information will be recorded at the DCC and provided to the central follow-up research staff. For data analysis outside the Data Coordinating Center (e.g., when a public access database is made available), the Data Coordinating Center will create a completely de-identified analytical database for use by the study investigators, and for final archiving. All PECARN study sites have been or will be offered Business Associate Agreements with the University of Utah. Copies of signed Business Associate Agreements are maintained at the Data Coordinating Center.

9.2 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 PECARN site participating in this trial. There will be no exclusion of patients based on gender, race, or ethnicity.

9.3 Conflict of Interest

NIH guidelines on conflict of interest will be distributed to all investigators. Conflict of interest review and any management plans necessary will be handled on a site-by-site basis, in compliance with each institutions policies and procedures and the NIH guidance.

10 Access to and 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)].

11 Data Sharing Plan

Per Federal regulations, the DCC will collaborate with the study investigators and NIMH to finalize public-use dataset procedures. This dataset will be prepared by the DCC, and will include adequate documentation to make the data useful to qualified investigators and the NIMH. This documentation will include a data dictionary, annotated forms, and brief instructions for accessing the data using standard statistical software. No user support will be provided by the DCC, PECARN or the study investigators for individuals who obtain the public use dataset for research. In accordance with NIMH requirements, the dataset and supplemental materials will be provided to NIMH 12 months after the final follow-up assessments are completed.

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