Improving Detection of STIs in PEDs ED: A Pragmatic Trial (Adolescent STI) PECARN Protocol Number 040

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PROTOCOL TITLE:

Improving Detection of STIs in PEDs ED: A Pragmatic Trial

Short Title: Adolescent STI
PECARN Protocol Number: 040

Lead Investigators and Authors:
Monika Goyal, MD, MSCE & and Jennifer Reed, MD, MS
Children's National Medical Center & Cincinnati Children's Hospital

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

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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Abstract

Sexually transmitted infections (STIs) are highly prevalent among adolescents. Despite established principles for STI control, clinical practices related to screening and diagnosis, treatment, and prevention of STIs among adolescents are suboptimal. There is an urgent need to expand our screening programs to nontraditional healthcare settings such as emergency departments (ED) to reach those adolescents who would otherwise not receive preventive healthcare, and to determine the most efficient and cost-effective method for providing this screening. The goal of this application is to leverage our recent insights obtained from single center ED-based adolescent gonorrhea and chlamydia screening research and apply them across a national pediatric ED research network to determine the most clinically effective and cost-effective screening approach for adolescents when implemented into a real-world clinical setting through a pragmatic trial. This will be accomplished through a network of childrens hospital EDs with a track record of robust research collaboration (Pediatric Emergency Care Applied Research Network or PECARN). This research will contribute to the evidence base for creating clinically effective, cost-effective, and sustainable Neisseria gonorrhoeae (GC) and Chlamydia trachomatis (CT)screening programs that can be successfully implemented into the clinical workflow of the ED. It will also improve diagnosis of asymptomatic STIs and decrease the time interval to treatment, consequently decreasing reinfection rates of transmission and the overall STI burden as well as decreasing healthcare costs. This intervention will rely on an innovative approach that electronically integrates patient-reported data to guide clinical decision support. This work is significant because it has the potential to shift current ED clinical practice paradigms from only acute health encounters to participation in the broader management of public health, and it will fill gaps in the literature needed to provide evidence for the best method of gonorrhea and chlamydia screening in an ED setting. First, we will apply human factors modeling methods to perform ED workflow evaluations at each participating pediatric ED to determine the most efficient way to integrate the screening process into everyday clinical care. Following these analyses, we will conduct a comparative effectiveness pragmatic trial of targeted STI screening (screening only those disclosing high risk sexual behavior) versus universally-offered STI screening (offered to all, regardless of risk) through electronic integration of patient reported data for provision of clinical decision support. We will then develop decision analytic models to evaluate the cost-effectiveness of targeted screening compared to universally offered screening. This research is novel in that it shifts the usual clinical practice paradigm in the ED from STI diagnosis in symptomatic adolescents to STI screening and prevention, an approach that is critical to addressing the STI epidemic among adolescents.

1 Study Summary

1.1 Hypotheses

The hypotheses of this study are:

1a. A higher number of GC/CT infections will be detected during implementation of universally- offered and targeted screening strategies when compared to usual care.

1b. The efficiency (cases detected/patients tested) of GC/CT detection will be higher during implementation of a targeted screening strategy when compared to a universally-offered screening strategy.

2a. Universally-offered screening will NOT be cost-effective compared with a targeted GC/CT screening approach when applied to the overall population of adolescents treated in emergency departments.

2b. Universally-offered screening will be cost-effective compared with targeted screening in adolescent emergency department populations with a high prevalence of GC/CT.

1.2 Specific Aims

This project has the following Specific Aims:

Specific Aim 1. To compare the effectiveness of usual care, targeted screening and universally-offered screening in EDs through a pragmatic trial that applies a human factors systems approach to implement GC/CT screening into routine clinical care.

Specific Aim 2. To determine the most cost-effective approach for GC/CT detection (i.e. usual care, targeted screening, and universally-offered screening) in an adolescent ED population.

1.3 Subject Eligibility, Accrual and Study Duration

Eligible participants will be identified by on-site study staff. Inclusion criteria are:

1. Males or females 15 up to and including 21 years of age.

Exclusion criteria are:

1. History of developmental delay; OR
2. Altered mental status; OR
3. Inability to provide consent for completion of the sexual health survey (SHS) and STI screening; OR

4. Critically ill; OR
5. Victims of sexual assult/abuse; OR
6. Unable to understand English.

2 Rationale and Background

2.1 Introduction

Adolescents are disproportionately affected by sexually transmitted infections (STIs)[1–3] and account for 9 million of the 19 million new STI cases annually.[2] The STI epidemic among youth is a national public health priority as noted in the Healthy People 2020 objectives, which specifically recommend enhanced STI diagnosis, treatment, and reduction in adolescents.[4] Failure to diagnose and treat STIs in a timely manner results in serious reproductive morbidity, mortality, and increased transmission of disease.

Adolescents frequently access the emergency department (ED) for care,[5–10] with the ED functioning as the primary source of health care for over 1.5 million adolescents.[9, 11, 12] EDs are potentially high-yield sites for the delivery of sexual health services as part of a larger public health prevention strategy. Although the Centers for Disease Control and Prevention recommend universal HIV screening in EDs,[13] no recommendations currently exist for gonorrhea and chlamydia (GC/CT) screening; thus <1% of the ED population is screened for GC/CT.[14] Addressing the effectiveness and integration of ED-based STI screening is critically needed.[15, 16]

Insufficient knowledge of the ideal structure for delivery (i.e. universally-offered or targeted to high risk groups) is a barrier to the implementation of ED-based GC/CT screening. While universally-offered screening (offered to all, regardless of risk) may detect a larger number of cases than targeted screening (screening only those disclosing high risk sexual behavior), it is more resource-intensive and may result in more false positive cases due to a lower pretest probability of infection. The Co-PIs, Drs. Goyal and Reed, are NICHD K23-funded investigators who are well-positioned to address this knowledge gap. They each study targeted (Goyal) and universally-offered (Reed) ED-based GC/CT screening via electronically entered patient-reported data providing real-time clinical decision support (CDS). They have shown that both strategies are acceptable, feasible, and result in increased STI screening rates at their respective pediatric EDs;[17–23] but it is unknown which method is most efficient and cost effective when instituted across a national sample of pediatric EDs with varying community STI prevalence.

The scientific premise of this application is to leverage our recent insights obtained from single center ED-based adolescent GC/CT screening research and apply them across a national pediatric ED research network to determine the most clinically effective and cost-effective screening approach for adolescents when implemented in a real-world clinical setting through a pragmatic trial. To be successful and sustainable, the ideal screening strategy must be easily incorporated into the clinical workflow. Electronic integration of patient-reported data with CDS offers one such solution with additional benefits: overcomes privacy concerns, circumvents provider biases about STI risk, and enables early detection of infection before development of adverse sequelae. The objective of this study is to compare targeted and universally-offered STI screening approaches by seamlessly integrating real-time CDS based on electronically-obtained patient-reported data into the normal ED workflow through human factors analysis followed by cost-effectiveness analyses. We propose to execute a multicenter comparative effectiveness pragmatic trial within a national sample of pediatric EDs through the Pediatric Emergency Care Applied Research Network (PECARN), a network of childrens hospital EDs with a track record of robust research collaboration.

2.2 Study Rationale

The Burden of Adolescent STIs: Although adolescents and young adults represent only 25% of the sexually active population, they comprise nearly 50% of all diagnosed STIs annually. Of the 19 million new cases of STIs each year, over 9 million occur among adolescents. Failure to diagnose and treat STIs in a timely manner can result in serious reproductive morbidity and mortality, including pelvic inflammatory disease, ectopic pregnancy, infertility, and facilitation of transmission of Human Immunodeficiency Virus (HIV). Most importantly, failure to diagnose STIs leads to increased transmission of disease, further increasing disease burden and contributing to the STI epidemic. The STI epidemic among youth is a national public health priority identified in the Healthy People 2020 objectives, which specifically targets enhanced STI diagnosis, treatment, and reduction in adolescents.

Current Adolescent STI Screening Rates are Low: There is a general consensus from the Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics, American College of Obstetrics and Gynecology, and the United States Preventive Services Task Force (USPSTF) for at least annual Neisseria gonorrhoeae (GC) and Chlamydia trachomatis (CT) screening in sexually active adolescents and young adults. However, a national survey of youth noted only 11% reported being tested for an

STI within the last 12 months. Many adolescents lack a medical home, placing them at higher risk for non-detection of STIs. More than one-third of adolescents do not report a source of primary care, and fewer than 15% of adolescents participate in yearly routine health maintenance exams. However, even when adolescents do access primary care, only 12% of sexually active females 15-24 years of age receive annual testing for GC/CT. Among high school youth with a routine health maintenance exam within the prior 12 months, less than half report having discussed STI, HIV, or pregnancy prevention at those visits. Despite STI screening being a HEDIS (Healthcare Effectiveness Data and Information Set) measure for health care quality and GC/CT screening considered to be one of the most beneficial and cost-effective preventive services among young females, it is also among the most underutilized.

The Emergency Department as a Strategic Venue for STI Detection and Treatment: The USPSTF has deemed preventive health services to be efficacious and cost-effective, and recommends that clinicians capitalize on all health visits, including acute care visits, to provide preventive services. The ED may be a particularly strategic venue for STI detection and treatment as adolescents comprise over 20 million ED visits annually and more than 1.5 million adolescents receive their only medical care through EDs. The CDC recommends annual GC/CT screening for all sexually active females <= 25 years of age and males who present to clinical settings with high prevalence of STIs. Adolescents, and specifically minority and non-privately insured adolescents, are more likely to access the ED than primary care offices for STI care. Although many patients do receive STI care in primary care settings, there has been a 17% decrease in adolescent STI visits in these settings, and a 10% increase in adolescent ED visits in recent years. Thus, the ED represents an additional setting for the provision of preventive services to supplement care provided in primary care settings, with subsequent linkage back to the medical home.

Current gaps in ED STI testing: Despite high rates of STIs in adolescents and that the ED often functions as the only access to health care for many youth, STI testing is not regularly conducted in the ED. Even when patients present with STI-related symptoms, the performance of sexual histories and STI testing are underutilized, leading to under-diagnosis and under-treatment. We previously reported that among adolescent females presenting to the ED with potential STI-related complaints, almost 20% did not have documented sexual histories or undergo STI testing. Sexually active and non-sexually active adolescents are interested in learning about sexual health in the ED setting, and a majority of adolescents presenting to the ED are accepting of STI testing, even when presenting for non-reproductive health issues. Currently, there are no pediatric EDs that

have implemented routine GC/CT screening into clinical practice. Rates of asymptomatic GC/CT screening outside of the context of research studies include <1% of the population. Therefore, if certain barriers to ED-based STI detection can be overcome, the ED may offer a strategic venue to address and improve the sexual health care of this high-risk population.

STI Screening vs STI Testing: There is often confusion as to what constitutes STI testing versus STI screening. Testing typically involves patients who are symptomatic or have a reason for testing, such as a recent known exposure. Alternatively, screening involves an asymptomatic population of patients. Furthermore, STI screening may use a universal approach where all adolescents are offered screening, or a more targeted approach, where only those with identified risk factors are screened.

Electronic surveys using patient reported outcome (PRO) measures may help overcome ED STI screening barriers: There is growing interest in the use of PROs in medicine as we strive to deliver patient-centered healthcare. PROs are defined by the FDA as any report of the status of a patients health condition, health behavior, or experience that comes directly from the patient instead of through another individual (e.g. healthcare provider, parent, etc.) and is not limited to health outcomes. Use of PROs leads to better communication and decision-making between healthcare providers and patients, and improves patient satisfaction and outcomes. The use of PROs to ascertain information about sexual health among adolescents is particularly appealing due to the sensitive nature of the topic. Adolescents cite privacy concerns as a potential barrier to disclosing sensitive health information in the clinical setting. Obtaining sexual health information confidentially in the ED can be challenging due to space/privacy issues, difficulty separating a patient from the caregiver in an acute setting, limited time, competing priorities, and lack of clinical comfort and training. Electronic-based surveys and interventions may obviate some of these barriers. Our previous qualitative work demonstrates that adolescents and caregivers cite improved confidentiality as one of the benefits of using tablet-based technology to offer STI screening in the ED setting. Electronic surveys not only provide a confidential method for obtaining sensitive health information, but they are also efficient and patient friendly, as they can be tailored to an individuals needs through the use of skip patterns and audio assistance. Adolescents do not require a separate room for an interview, and thus, the surveys can be administered while they are awaiting clinical care. This method is also provider friendly and allows for an efficient way to ascertain sensitive health information.

Clinical Decision Support (CDS) can improve patient and process-oriented outcomes: CDS can be used to aid clinicians and patients in making healthcare decisions.

CDS facilitates shared decision-making using patient-specific data and clinician decision aids. In a systematic review of over 70 randomized controlled trials of CDS, improvement in clinical practice was seen in 68% of the included studies. When applied effectively, CDS increases quality of care, enhances health outcomes, helps avoid errors and adverse events, improves efficiency, reduces costs, and boosts provider and patient satisfaction.

Targeted vs. Universally Offered STI Screening for the ED setting: Although the CDC recommend universal HIV screening in EDs, there are currently no recommendations for GC/CT screening. Both existing research and expert consensus support the need for research addressing the effectiveness, sustainability, and integration of ED-based STI screening programs. Determining the best screening strategy (universally-offered or targeted testing of patients at risk for STIs) for the ED setting requires further investigation. Universally offered screening provides many benefits: it removes patient stigma, circumvents provider biases about STI risk, eliminates questions regarding sexual activity, results in early detection of infection prior to the development of adverse sequelae, reduces the public health burden of STIs, and provides opportunities for risk-reduction counseling. Universally offered STI screening also eliminates many of the barriers to current STI detection in an ED setting, including practitioners who may lack the time to address sexual health among patients presenting with non-STI related complaints. However, due to the additional costs of testing a larger number of individuals at low risk, universally offered screening may not be cost-effective compared with a targeted approach. A universally-offered screening approach may also result in a higher false positive rate due to a lower pretest probability of infection. This can result in greater downstream costs associated with confirmatory testing, exposure to unnecessary antibiotics, and potentially avoidable emotional distress. Therefore, targeted screening may share many of the benefits of universally offered screening with respect to increased asymptomatic detection, removal of patient stigma, opportunities for risk-reduction counseling, and efficiency, but overcome some of the potential disadvantages. Regardless, in order to be successful and sustainable, the ideal screening strategy must be easily incorporated into the clinical workflow of busy EDs. Electronic integration of PROs in combination with healthcare provider CDS offers one such solution.

Integrating PROs with the EHR for CDS: We propose to engage in health process redesign and use electronic surveys with EHR integration and CDS to efficiently and effectively improve clinical care in the ED and evaluate the most effective approach to GC/CT screening. Practice-based research is a necessary step before implementation of a new strategy into practice. Thus it is important to integrate the traditional forms of research with health system redesign methods to translate discoveries from laboratory

to patient and ultimately to the health care delivery system.[24–26] Through the Co-PIs individual K23 awards, Drs. Goyal and Reed have demonstrated that patient-reported data can successfully be used to provide CDS to ED clinicians leading to an increase in GC/CT testing rates.[17, 22] Implemented independently, these two methods (PROs and CDS) have proven successful in various ED and general pediatric clinical and process improvement projects.[27–31] To our knowledge, using health process redesign methods to incorporate electronic PRO measurements into the EHR for the provision of real-time CDS has not been used in implementing screening programs in an ED setting. CDS features identified to be most important for improving clinical care include integration with the electronic order entry system, request for documentation of reason for not following system recommendations, and provision of the CDS at the time and location of decision making.[32] All of these features of CDS will be included in this proposal in addition to conducting human factors workflow analyses at each participating ED for site-specific adaptations. Integrating these CDS features will allow us to be optimally poised for an accurate comparison of the different GC/CT screening strategies. Furthermore, the knowledge gained from workflow analyses at each participating site may help inform the implementation of STI screening at other EDs and across other clinical settings. Our long-term hypothesis is that using this novel system redesign to evaluate the effectiveness of universally-offered versus targeted GC/CT screening interventions in the ED will lead to an evidence-based approach that will ultimately decrease the overall rate of infected adolescents. If this hypothesis is correct, large-scale ED-based GC/CT screening interventions could be implemented to strengthen the potential impact of the ED health system on population health. Using these methods will enable us to integrate an effective GC/CT screening method into the daily routine of an existing health care system. Furthermore, if the aims of this research are successful, it has potential to serve as a model for other ED-based screening interventions.

Scientific Premise: Although the ED can serve as a critical venue for the detection and treatment of STIs, the optimal STI screening strategy (targeted vs universally-offered) has yet to be determined. Therefore, the scientific premise of this application is to leverage our recent insights obtained from single center ED-based adolescent GC/CT screening research and apply them, through a pragmatic trial, across a national pediatric ED research network to determine the most clinically effective and cost-effective screening approach for adolescents when implemented in a real-world clinical setting.

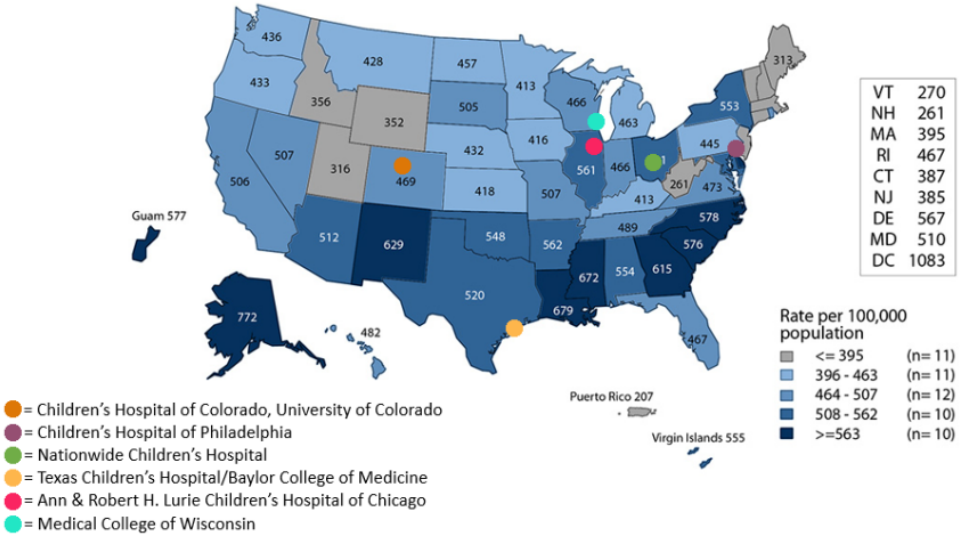

Figure 1: Rates by State.

3 Overall Study Design

3.1 Study Setting

The study will be conducted at each of the 6 participating PECARN pediatric EDs, which include Nationwide Childrens Hospital (Columbus, OH), Childrens Hospital of Philadelphia (Philadelphia, PA), Lurie Childrens Hospital (Chicago, IL), Childrens Hospital of Wisconsin (Milwaukee, WI), Denver Childrens Hospital (Denver, CO), and Texas Childrens Hospital (Houston, TX). These sites provide geographic diversity while allowing us to explore these STI screening approaches in high and low prevalence states (see Figure 1)[3] Each site has the Epic (Verona, WI) EHR and the IT resources to support this study. All the sites will be monitored under PECARN and the Data Coordinating Center (DCC) with individual site PIs and research coordinators (RC) designated at each institution.

3.2 Study Sample

The study staff will perform observations of adolescents seeking care in the ED who meet eligibility criteria. Male and female patients 15 through 21 years of age will be included regardless of their chief complaint, and only those patients who are unable to understand English, who are critically ill, who are victims of sexual assault or abuse, have cognitive impairment or altered mental status, or who would be unable to provide consent for

completion of the SHS and STI screening will be excluded. The study population will be limited to those patients available from the six sites during the specified collection time periods.

3.3 Workflow Evaluations

The study research team will work with the sites to create ED workflow evaluations to determine:

1. How best to integrate a new pathway in the EHR.

2. How best to integrate the new workflow of approach and consent in the Emergency Department.

3. How best to integrate the use of the tablet in the workflow.

3.4 Pragmatic Trial

We will conduct a comparative effectiveness pragmatic trial using a stepped wedge crossover design.[33] A stepped wedge design involves the sequential roll-out of an intervention or a sequence of interventions to individuals or sites over multiple time periods. At the end of the study, all sites will have received all interventions, but the order in which sites are enrolled is randomly assigned. Once the final intervention is implemented, that intervention will continue until the end of the study. We considered many alternative study designs and concluded that the stepped wedge crossover design is most appropriate for this study as it will allow sites to act as their own controls, thus increasing efficiency of the study, and allowing us to examine the effect of time on the effectiveness of an intervention. This is important because in real-world clinical settings, adoption is not 100% and does not occur instantaneously. The design also allows us to control for the effects of secular trends (e.g. changes that are outside the interventions of the study). We have designed this as a pragmatic trial because we want to evaluate the performance of these screening strategies in routine clinical care, rather than under strict experimental conditions.

Figure 2 presents an example step wedge design. Actual implementation may differ, but the general principals will be maintained. Sites will be randomized to one of these six positions. Each time period, labeled 1 through 52, is a 2-week block of time. Using the stepped wedge design, each site will first begin baseline data collection (B) for a minimum of 8 weeks. After collecting baseline data, each site will subsequently be randomized to either start with implementation of a targeted screening intervention (T) or a universally

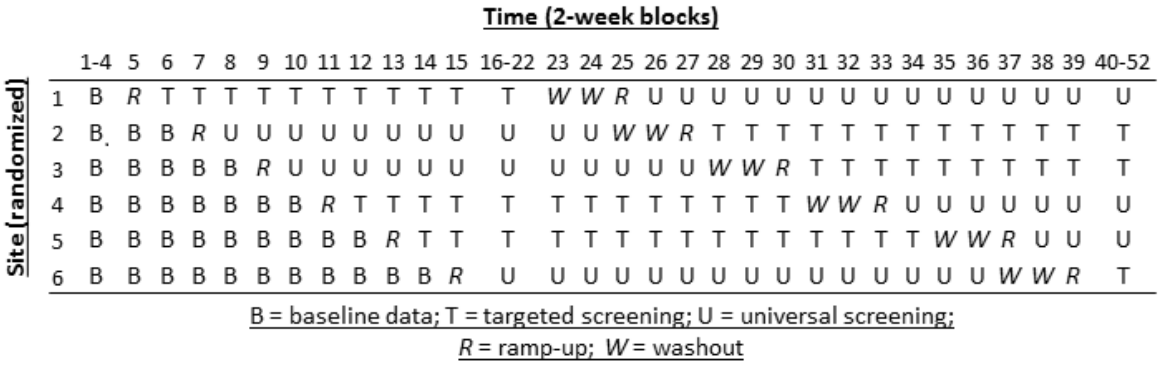

Figure 2: Stepped Wedge Design.

offered screening intervention (U). Each site will then cross-over and implement the opposite strategy. The final intervention will continue until the conclusion of the study. We will include a 4-week washout (W) period between interventions during which we will stop the intervention completely before starting the next intervention. Additionally, the first 2 weeks of each intervention will be considered a ramp-up period, and will be excluded from data analysis.

3.5 Cost-effectiveness analysis

Even if clinical strategies, such as universally offered screening for STIs, are proven to be effective, the costs of those strategies compared with usual care or more targeted approaches may make them impractical and unsustainable in a cost-constrained healthcare system. Cost-effectiveness analysis is a commonly used tool that allows policy makers and clinicians to measure the benefits gained for the additional costs of such strategies. The result of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER), which describes the additional cost of the more expensive but more effective strategy being examined, in this case universally offered STI screening, compared with the lesser cost of the less effective strategy (we have hypothesized this will be targeted screening) divided by the measure of effectiveness being considered. The most commonly used metrics in the peer-reviewed medical literature examine the incremental cost per quality-adjusted life year (QALY) gained; however, any meaningful measure of effectiveness can be used. For this project, we plan to look at additional cost per STI detected, as well as cost per QALY gained. We will develop decision analytic models (using Markov state transition structure) to evaluate the cost-effectiveness of universally offered screening compared

with targeted screening. To be complete, we also will include usual care as a third strategy. A simple model will only examine effectiveness in terms of STIs detected. A more complicated model will include short- and long-term consequences of treated and untreated disease. Short-term outcomes will include the likelihood of follow-up and treatment once a diagnosis has been made, along with the efficacy of antibiotic therapy. Based on test characteristics from the literature, small numbers of patients may have false positive or false negative test results. We will model the consequences of both, in terms of additional costs and consequences of unnecessary treatment for false positives, and the costs and consequences of undetected/untreated STI in the case of false negatives. Outcomes also will be modeled for unscreened patients who later return for treatment of symptomatic disease (e.g., acute pelvic inflammatory disease). Long-term outcomes addressing the sequelae of untreated/ undetected STIs (tubal infertility, ectopic pregnancy, and chronic pelvic pain) and outcomes following successful detection and treatment will be modeled. Data generated from Aim 2 regarding the effectiveness of the two screening strategies in detecting GC/CT, the proportion of identified patients who ultimately receive treatment, and the prevalence ranges of GC and CT in cohorts presenting for ED care at the 6 sites in our study, will be used to inform probabilities in the model. Literature-based estimates will inform other probabilistic events and costs of long-term STI sequelae in the model. Incremental cost-effectiveness ratios will be calculated to determine cost-effectiveness. The analysis will use a health care sector perspective[34] that includes medical costs borne by third-party payers and paid out-of-pocket by patients. These will include current and future costs related to both the intervention and downstream events related to treated or missed STIs. We will perform a series of deterministic sensitivity analyses to explore the impact of parameter uncertainty on results, and known population variations. A key parameter of interest is the background rate of STI. This likely varies from location-to-location, and will be a key determinant to the cost-effectiveness of the universally offered screening strategy. We will calculate the threshold of background STI prevalence above which universally offered screening becomes very cost-effective (i.e., an ICER <$50,000/QALY). As a result, the cost-effectiveness of the universally offered screening strategy may vary from location to location in the study, and in real-world use of the screening tool. Understanding this threshold may help shape policy for optimal screening strategies in different locations and settings.

4 Study Procedures

Human Factors Workflow Analyses: Human factors workflow evaluations will occur at each of the 6 participating sites. A convenience sample will be obtained during the times of CRC availability. These observations will be conducted to understand

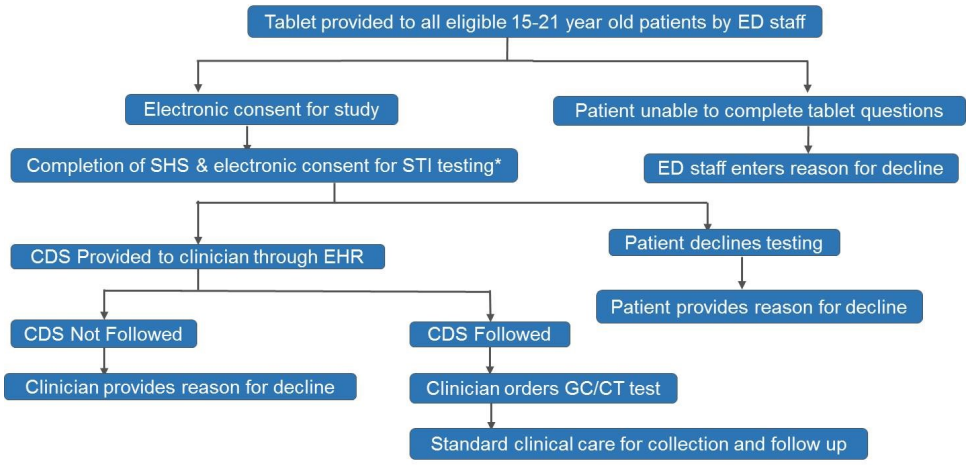

Figure 3: Study Design.

site-specific ED flow differences that may occur with respect to the care of adolescents. We will collect observational data regarding ED workflow and information exchange using the tool TaskTracker[35] to record clinical workflow and identify common workflow paths.

Pragmatic Trial: Once the ideal workflow strategy is identified at each individual site, all participants in both the targeted and universally offered screening phases will use a handheld tablet device to provide electronic informed consent for participation. All participants will complete the previously developed and validated ACASI SHS containing questions regarding their personal sexual health history.[36] The PROs tool will risk-stratify patients for STIs based on their reported sexual experience and/or presence of STI-related symptoms. Using the tablet device, patients will also indicate their interest for clinician-ordered STI testing (urine-based GC/CT). This will provide clinicians real-time EHR-integrated decision support for GC/CT testing.

4.1 Screening and Enrollment

Since this is a pragmatic trial, the exact process of distributing tablets may differ by site and will be further clarified during the workflow analyses. At some sites registration staff may be responsible for tablet distribution and at other sites triage or bedside nurses may distribute the tablets. This will depend on the results of the workflow analysis. The electronic informed consent document will contain information about the study. Should questions arise, RCs will be available to answer more detailed questions. Research staff are available at each participating ED up to 16 hours per weekday and between 8-16

Patient Classification	CDS
At High Risk	STI Testing Highly Recommended
At Risk	STI Testing is Recommended
At Low Risk	STI Testing Not Necessary at this time

Table 1: STI Testing CDS

hours on weekends. During hours without RC presence, there will be a research-trained clinical provider (with both protection of human subjects and good clinical practices (GCP) training) present to answer questions. Reasons for not offering the tablet will be recorded by the ED staff. Furthermore, if adolescents decline study participation, a reason for refusal will also be recorded on the tablet.

- **Targeted screening**: During the targeted screening intervention, data from the SHS will be integrated into the EHR and will provide CDS for GC/CT testing based on SHS-calculated STI risk (developed and validated by Dr. Goyal). Patients will be classified as at high risk for STIs if they disclose being sexually active and have either the presence of STI-related symptoms or any of the following high risk behaviors: more than 1 sexual partner in the last 3 months, no condom use during last sex or prior history of STI. Patients will be classified as at risk if they disclose being sexually active but do not disclose having any STI-related symptoms or any high-risk sexual behaviors. Patients will be classified as at low risk if they deny any history of sexual activity (see preliminary data for STI positivity rates by risk strata). When patients classify as at high risk, clinicians will receive CDS that STI testing is highly recommended; when they care for patients who classify as at risk, they will receive CDS that STI testing is recommended; when caring for patients who classify as at low risk, they will receive CDS that STI testing is not necessary at this time. If the clinician chooses to follow the recommendation for screening based on patients risk assessment, and the patient consents to testing on the tablet device, urine GC/CT testing will be performed.

- **Universally offered screening**: During the universally offered screening intervention, STI screening will be offered to all eligible adolescents, regardless of risk. All eligible patients will also complete the SHS, will be informed of the CDC GC/CT testing recommendations and then be given the option to decline STI testing using the tablet device. During this phase, the SHS results will not be available to the clinician. STI testing recommendations will be based only on the patients decision to undergo GC/CT testing. Like the process followed in the targeted screening phase, if the clinician follows the CDS that informs the clinician that the patient

agreed to GC/CT screening and consequently orders testing, urine GC/CT testing will be performed.

- **Both approaches**: If the patient is at risk for STIs and declines GC/CT testing, or the patient simply declines GC/CT testing on the tablet but the clinician believes the patient should be tested, the clinician will have the opportunity to engage in a shared decision-making process with the patient as per routine clinical care. Alternatively, if the clinician declines the CDS GC/CT testing recommendations, he/she will be asked to electronically document the reason the CDS is not being followed. All patients who test positive for an STI will be notified of their results and provided treatment based on each sites standard clinical processes for result notification and treatment. Among all patients tested for GC/CT, the associated primary care clinician (PCP) will be informed of the testing and results via existing communication methodologies including Epic in-basket messages, faxes, or other electronic communication methods, and both patients and clinicians will be encouraged to schedule outpatient follow-up appointments. Medical staff, including faculty, clinical trainees, nurses and other medical support staff, will be educated about each screening intervention prior to implementation and with frequent reminders, through in person staff meetings, emails, and Epic job aids.

4.2 Surveys

All data entered into the tablet by either the ED personnel or the patient will be stored at the study site. This information will include the patients medical record number, encounter ID, patients electronic consent to participate in the study, and survey responses. For those patients who either do not meet inclusion criteria or refuse participation, exclusion/refusal reasons will be documented by the staff and/or patients electronically and stored in this database.

During implementation of the targeted screening intervention, the patient responses to the SHS survey will categorize patients as at high risk, at risk, or at low risk for STIs. This composite score will then be transmitted to the EHR through the Bridges Interconnect system, a secure native interface allowing one-way transmission of data into Epic. Bridges Interconnect is used to send data outside the Epic EHR into the EHR and is available at all participating sites. CDS will be triggered on the EHR based on STI risk strata as calculated by the SHS. During implementation of the universally offered screening, CDS for GC/CT screening will be determined by the patients decision to be screened. If a patient agrees to GC/CT screening, that information will be transmitted to the EHR through the Bridges Interconnect system, which will then trigger GC/CT

screening CDS for the clinician.

5 Data Analysis

5.1 Specific Aim Analyses

Specific Aim 1. To compare the effectiveness of usual care, targeted screening and universally-offered screening in EDs through a pragmatic trial that applies a human factors systems approach to implement GC/CT screening into routine clinical care.

Human Factors Workflow Analyses: Data will be aggregated across observations and workflow analysis will be performed to identify the most frequent tasks and interactions during an ED visit. Transition diagrams will be created to examine overall workflow processes which will include tasks performed, communication events between clinicians and patients, and interactions with technology. Common patterns of activity will be identified and used to inform deployment of the application to the patient and integration with the EHR.

Pragmatic Trial: We will report descriptive statistics to summarize each primary and secondary outcome variable. Our primary comparison of GC/CT screening strategies will be targeted vs. universally offered. We will compare detection rates (number of STIs detected divided by the number of eligible, asymptomatic patients) using site 2-week period as the unit of analysis. Standard stepped-wedge analysis techniques will be used. Specifically, the site detection rate over each 2-week period will be the outcome in a linear model to examine the effect of screening strategy on detection rate. In the model, we will include a fixed effect for each site. To control for temporal trends, we will model the effect of time as a piecewise linear function with 8 three-month segments (i.e., cutpoints at the following times on the two-week scale: 0.5, 7, 13.5, 20, 26.5, 33, 39.5, 46, and 52.5 weeks). A three-level intervention effect will be included, and we will test for a difference between targeted and universally offered screening at a 5% significance level. We will perform a similar analysis using the outcome of rate of positivity among those tested for GC/CT. We will also calculate the proportion of visits during which eligible patients agreed to GC/CT testing and compare them across the 2 STI screening strategies (targeted vs. universally offered). We will calculate the proportion of visits during which clinicians follow the GC/CT testing CDS recommendations across the 2 GC/CT screening strategies and will perform multivariable logistic regression to identify patient, clinician, and site-specific factors that may be associated with uptake of the CDS.

As additional secondary outcomes, for patients who consent to SHS completion, we will perform multivariable logistic regression to identify demographic and behavioral factors associated with GC/CT testing consent and GC/CT positivity.

Specific Aim 2. To determine the most cost-effective approach for GC/CT detection (i.e. usual care, targeted screening, and universally-offered screening) in an adolescent ED population.

Cost-effectiveness analysis: Markov state transition models will be built using readily available software (Decision Maker, Boston, MA). Health states will include those that impact prognosis, cost and quality of life, such as asymptomatic and symptomatic infection with GC and/or CT, pelvic inflammatory disease, infertility, ectopic pregnancy, and chronic pelvic pain. Because the median ED LOS for an adolescent is 4.25 hours, and we have previously demonstrated no significant difference in LOS between patients who completed the SHS compared to those who did not,[17] time to complete survey will not be entered into the model. Furthermore, during a 4-hour ED visit, there is ample time to collect a urine sample, and urine testing is often already requested for clinical care. Therefore, time to obtain samples will also not be included in the cost analysis. We will use a one-month cycle length and a life-long time horizon. Patients will move between health states over time depending upon events that occur in each one-month cycle of the simulation. Health states and events will have associated quality of life and costs. We will perform analyses first using base case estimates for all parameters. We will next perform deterministic sensitivity analyses, examining key parameters one, two, or three at a time, to explore the impact of uncertainty and to address other plausible scenarios, such as populations with lower or higher prevalence of STIs. We also will be able to test various cut points for the STI risk prediction tool, described in aim 2, to see if there is an optimal cut point that minimizes the incremental cost-effectiveness ratio, finding the best balance between sensitivity and specificity for the risk prediction tool. Finally, we will perform probabilistic sensitivity analyses, using second order Monte Carlo modeling, to generate cost-effectiveness acceptability curves, providing further insights into the proportion of the time that the winning strategy will be cost-effective.

5.2 Sample Size Calculations and Statistical Power

Workflow Analyses: We estimate that we will observe between 20-30 individuals per site, which is a common sample size for studies of ED workflow processes.

Difference	Power
0.5%	80%
0.75%	98%
1%	99%

Table 2: Power Calculations

Pragmatic Trial: We plan to enroll at 6 PECARN sites. Based on PECARN data, with 6 sites for 52 two-week periods, we conservatively anticipate that approximately 288 patients or more per two weeks per site will arrive. Of these, we conservatively expect to enroll 242 per site. About 220 of these will be asymptomatic and included in the primary analysis. Our preliminary data reveal STI screening rates of 0.16% (usual care) leading to detection rates less than 0.02%. Asymptomatic STI detection rates range from 4-10% in a population of universally offered screening. In a targeted population, which makes up about 1/3 of the overall asymptomatic population, 10-14% will test positive. This leads to estimated detection rates of approximately 3-5%. For power calculations, we assume a detection rate of 4.5% using a targeted strategy and a standard deviation in rates across sites of 2%. Based on expected enrollment of 220 asymptomatic patients per time period per site, we will have approximately 99% power to detect a 1% difference in detection rates, and over 80% power to detect a difference as small as 0.5% between targeted and universally offered strategies (see table above). A 1% difference in detection corresponds to approximately 450 additional STIs detected per year at these sites alone. If results from this study inform screening at centers across the country, the numbers captured could be orders of magnitude higher. Additionally, we will also have adequate power for subgroup analyses based on gender, age, race/ethnicity, and symptomatology, as the design will provide over 90% power to show a difference in detection rates of 2% for subgroups as small as 40 patients per month. Confidence intervals around detection rates in each of the screening strategy groups will be smaller than +/- 0.3%.

Cost-Effectiveness Analysis: The sample size for the pragmatic trial will drive the uncertainty around parameter value estimates for disease prevalence and the effectiveness of the two strategies in diagnosing STIs among patients with asymptomatic infection. We expect to estimate detection rates within approximately 0.25%. The number of cases detected and not detected in both strategies will be used to parameterize beta distributions in the probabilistic sensitivity analyses.

6 Data Management

6.1 Clinical Site Data Management

Each clinical site will maintain any research records in locked filing cabinets and/or password protected locations. The site will maintain an Essential Documents Binder, which may be in paper or electronic form. Copies of all informed consent documents will be kept on file and be available for site monitoring inspection (on site or remote).

6.2 Electronic Data Capture System

The Data Coordinating Center (DCC) will develop an electronic data capture system for this trial. Currently the DCC uses multiple applications, such as OpenClinica or REDCap, and will elect to use the most appropriate application at the time of implementation of the study. Data will be entered by each clinical site.

The DCC will use an electronic discrepancy management system to notify sites of inconsistent or erroneous data entry, which will be corrected by the clinical site. The discrepancy management system maintains an audit trail of all discrepancy resolution.

All study information requiring EHR abstraction will be accessed through Epics Clarity, a SQL-based querying tool available to all Epic sites. Data will include the patients medical record number, encounter ID, demographics, STI orders, GC/CT results, and information associated with the firing of the CDS (i.e. user, actions taken, time fired, refusal reasons for the clinician not following the CDS), and follow up treatment data. In addition to GC/CT test results, we will also abstract test results from any other STI test that may have been ordered by the clinician, including testing for Trichomoniasis, Herpes Simplex Virus, Syphilis, and HIV. These data will be merged with the tablet data using the patient encounter ID for all adolescents who agree to participate.

Data will be abstracted daily during study implementation for quality checks and then weekly via a CSV file. The data manager at each site will compile the data through this automated process and results will be stored securely, accessible only by study staff. The data from the application database and EHR database will be automatically merged by matching the patient encounter IDs as a unique identifier. SQL code for this automated merge was developed by Dr. Dexheimer at CCHMC and will be shared with each site. The merged data at each site will then be stripped of patient names and a unique study ID number will be attached to each encounter. This unique study ID will allow linkage of the databases to allow for confirmation of data in the event of data queries from the DCC. The study team will develop a Manual of Operations for participating sites which will include creation of data dictionaries, data transfer instructions, methods of encryption

and confidentiality requirements. Sites will export data monthly, and data cleaning and quality assessment of each month's data period will be completed prior to the data merge and transfer to the DCC.

6.3 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous Pediatric Emergency Care Applied Research Network studies, and we will utilize this process to ensure excellent quality data in the proposed study. Study monitors must be provided with appropriate 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 study monitor's review of data in the electronic medical record.

6.3.1 Site Monitoring Plan

A supplemental study-specific risk-based 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.

6.3.2 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 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 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.

6.4 Data Coordinating Center

6.4.1 Data Center Description

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1400 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 99% of its environment. The virtual environment consists of more than 200 virtual servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware of software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages

over 50 terabytes of data. The storage solution consists of Dell's EqualLogic PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture is no longer be a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running 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. DCC storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

DCC information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

6.4.2 Security and Confidentiality

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us 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 2012 domain servers. Communication over public networks is encrypted with virtual point-to-point sessions using transport layer security (TLS) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the TLS protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2012 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. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

6.5 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 (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) for each study site.

7 Protection of Human Subjects

7.1 Institutional Review Board (IRB) Approval

The Data Coordinating Center and each clinical center must obtain approval from their respective IRB prior to participating in the study. A central IRB (cIRB) at the University of Utah will be used for this study. The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

7.2 Waiver of Authorization

A waiver of authorization is requested in order to be able to pre-screen/establish eligibility for subject prior to approaching, consenting, and enrolling a subject.

Human Factors Workflow Analyses: We are requesting a waiver of documentation of written consent for Phase 1 as the workflow analyses are minimal risk and no identifying information will be collected (no PHI). An information sheet will be provided to explain why staff is outside the patient room and what information is being collected. Only timings of and type of interaction with healthcare providers will be recorded by the research staff.

Pragmatic Trial: While adolescents <18 years will be encouraged to share study participation with parents and/or guardians, a waiver of parental permission will be requested as these participants are seeking confidential health services. Minors in all participating institutions are able to consent for testing and medical treatment related to STIs without parental permission based on state laws. Under 45 CFR 46.408 (c), an IRB has the authority to legally waive parental permission if it determines that a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, an appropriate mechanism for protecting the children who will participate as research subjects is substituted, and that the waiver is not inconsistent with Federal, State, or local law.

7.3 Waiver of Documentation of Informed Consent

For the pragmatic trial, all adolescent patients meeting inclusion criteria who present to the ED will be eligible for the study. Patients approached for survey completion via tablet

will complete an electronic consent prior to survey administration. When handed the tablet, the first page will include a study information sheet. All participants, through the electronic survey will provide electronic consent. We are requesting a waiver of written documentation of informed consent/assent for these participants. This project meets the requirements for a waiver of documentation as outlined in 45 CFR Part 46.117 in that the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting in a breach of confidentiality. This research presents no more than minimal risk to the subjects. Furthermore, state law allows adolescents to consent for treatment related to sexual health. Therefore, a waiver of parental consent will be requested in compliance with state law as well as to preserve the confidentiality of study participants. It is standard of care for health care providers to interview adolescents privately, without the presence of a parent or guardian. Additionally, it is standard of care for adolescents to be provided confidential care for reproductive or sexual health issues. Furthermore, obtaining written informed consent could place study participants at even greater risk for breach of confidentiality as a written document would now associate the teen with participating in a study related to sexual health.

7.4 Waiver of Informed Consent for Chart Review

Waiver of consent is requested for observational data collection for each patient eligible for this study. We are requesting data on all STI testing performed for all patients who meet inclusion criteria as part of a chart review. This information will be abstracted in aggregate form and no identifying information will be collected. This will be to measure STI testing rates and STI prevalence among each site during each intervention.

The justification for waiver of consent for the observational data collection in this study is based on the following factors:

1. The scientific validity of the study is dependent on capturing all eligible patients during the period of study, as one of the major goals is to accurately describe the characteristics of the entire eligible population.

2. The study involves no intervention and collection of observational data will not require any patient or parent contact.

3. The minimal risk of loss of privacy is mitigated by secure data management at the DCC, and analysis datasets will be de-identified.

7.5 Potential Risks

There is a minimal risk of loss of confidentiality of the subject is a potential risk of the study; however, safeguards are in place to protect against this.

7.5.1 Improper Disclosure of Medical Information

At each site, the investigators and study staff involved in the study will have access to PHI about some or all subjects. All data will be submitted electronically using a secure system hosted by the Data Coordinating Center. At the DCC, the DCC PI, data managers, statisticians, and other staff may have access to a limited set of identifiable information.

7.5.2 Medical Risks

There are no known or anticipated additional medical risks from participating in the trial.

7.5.3 Social Risks

Because sexual health and STIs can be a sensitive subject, some adolescents may feel embarrassed discussing the topic and thus may refuse to participate in the STI screening interventions. Unlike an adolescent clinic or other primary care setting in which parents may be comfortable giving their adolescent privacy during his/her health care visit, the ED setting is more challenging in this respect as many patients present with acute issues accompanied by their parents. Furthermore, the ED is not always conducive to conducting confidential health interviews with patients due to ED design and space limitations. However, state laws support confidential STI screening for all adolescents, and previous parent and adolescent qualitative data has shown that a tablet-based approach is highly preferable when offering STI screening. Therefore, computerized surveys can help overcome the space-related challenges and confidentiality related to sexual health assessments in the ED. Based on our preliminary work, which has demonstrated high rates of STI screening acceptance and interest among adolescents seeking care in the ED[18–20]18 we do not anticipate this to be an issue.

7.6 Protections Against Potential Risks

7.6.1 Improper Disclosure of Medical Information

Loss of confidentiality will be mitigated by the use of the Data Coordinating Center which has a highly secure IT infrastructure, and by the existence of trained research staff at participating sites. Data will be housed at the DCC where all files are protected and

where all personnel at the DCC have undergone training and have signed confidentiality agreements. The investigators and staff of the DCC are fully committed to the security and confidentiality of data collected for the study. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with the DCC data systems have received Human Subjects Protection and HIPAA eduction. Each site will be responsible for ensuring that appropriate data security procedures are in place.

7.6.2 Social Risks

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.

7.7 Potential Benefits

The potential benefit from participation in this study is that participation may lead to the detection and treatment of undiagnosed STIs.

8 Data and Safety Monitoring Plan

8.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise the sponsors and Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual Clinical Center, review of serious adverse events and other subject safety issues, and review of formal interim statistical analyses of treatment efficacy.

9 Study Training

9.1 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, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, protection of human research subjects, 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 will be the main contact for study questions.

10 Regulatory Issues

10.1 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de–identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de–identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

10.2 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

10.3 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

10.4 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)].

10.5 Public Use Data Set

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

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