PennState

HRP-591 - Protocol for
Human Subject Research

Protocol Title:
HPV ECHO: Increasing the adoption of evidence-based communication strategies for HPV vaccination in rural primary care practices.

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University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Penn State Health:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

To evaluate the effect of two Project ECHO-delivered human papillomavirus (HPV) vaccine communication interventions in primary care clinics on HPV vaccination rates.

1.2 Primary Study Endpoints

The primary study endpoint is HPV vaccine initiation (≥1 doses) among adolescents, ages 11-14, between baseline and 12-month follow-up at the clinic level.

We hypothesize that (H1) both ECHO interventions (HPV ECHO and HPV ECHO+) will increase vaccination compared to the control but (H2) vaccination rates will be highest for clinics receiving HPV ECHO+.

The three study arms are:
1. HPV ECHO: This intervention will use the Project ECHO model to connect experts on vaccine communication and cancer prevention with healthcare providers in rural primary care practices in Pennsylvania to improve best-practice communication about HPV vaccine. Participants will participate in 8 one-hour telementoring sessions and will bring de-identified case studies about parental vaccine hesitancy to discuss during sessions with the group of experts. Sessions also include a brief lecture focused on the Announcement Approach, a best-practice communication for HPV vaccination.
2. HPV ECHO+: This intervention will provide the telementoring training as HPV ECHO plus a systems strategy, which comprises a recall notice to notify parents that their child is behind for HPV vaccination and address their primary reason for not vaccinating.
3. Control: Participants in this arm will be a wait list control and will receive access to the recording from all eight ECHO sessions at the end of their wave.

1.3 Secondary Study Endpoints

Secondary study endpoints #1 (effectiveness) are HPV vaccine initiation by gender, for 15-17 year-olds, up-to-date HPV vaccination, concomitant vaccination for Tdap and meningococcal vaccines, and vaccinations at interim time points (i.e., 3-, 6-, and 9-month follow-up).

We hypothesize that (H1) both ECHO interventions will increase all vaccination secondary endpoints compared to the control but (H2) vaccination rates will be highest for clinics receiving HPV ECHO+.

Secondary study outcomes #2 (implementation) are cost, acceptability, appropriateness, adoption, penetration, and sustainability to healthcare providers.

We hypothesize that (H3) clinics receiving HPV ECHO+, as the most resource-intensive intervention, will incur higher overall costs but lower cost per additional vaccine dose delivered. We also hypothesize that (H4) providers in both intervention arms will report equally high satisfaction with (acceptability) and perceived fit (appropriateness) of ECHO-delivered interventions, greater use (adoption) of best practices, staff engagement (penetration), and maintenance of practice changes (sustainability). These outcomes will be evaluated in the two intervention arms only.

Secondary study outcome #3 (secondary acceptance) is HPV vaccine initiation (≥1 dose) after initially declined at the clinic level.

We hypothesize (H5) that clinics receiving HPV ECHO+ will have higher secondary acceptance rates than those in the HPV ECHO arm. This outcome will be evaluated in the two intervention arms only.

Secondary study outcome #4 (nested study) is to explore the level of exposure to and impact of vaccine information from intervention arms versus naturally-occurring sources (e.g., social media). In the nested study, we will follow a subset of 211 HPV vaccine-declining parents for up to 12 months. Only Penn State Health clinics that are enrolled in the study will be invited to participate in the nested study. The nested study is exploratory and has no hypothesis.

2.0 Background

2.1 Scientific Background and Gaps

The safe, highly-effective human papillomavirus (HPV) vaccine remains underused in the US; only 51% of 13-to 17-year-old girls and boys were up-to-date by 2018.[1] Rural populations are particularly impacted, with 15% lower rates of vaccination.[1] The Announcement Approach is effective in increasing HPV vaccine uptake during the clinic visit by training providers to make strong vaccine recommendations and answer parents' common questions.[2] However, the training is limited to a single 60- to 90-minute, in-person session delivered by one physician educator and offers standardized scenarios for providers to practice their communication skills, mostly by memorizing and reciting messages. Systems communication like recall notifications also improve vaccination by reducing missed clinical opportunities.[3] However, these recall notifications have not been tested in combination with the Announcement Approach training to supplement provider communication with parents. Also, rural providers, especially family practice physicians, are less likely to strongly recommend HPV vaccine and implement systems strategies to improve vaccination.[4-6] Past HPV vaccine communication studies tend to focus on large urban clinics; in turn leaving rural clinics behind.[7] These data prompt the question: "How can academic centers support HPV vaccination in rural primary care clinics?"

Although never tested to support HPV vaccination, the ECHO (Extension for Community Healthcare Outcomes) Model is a proven implementation strategy to promote capacity exchange between health care experts at academic centers ("the hub") and primary care providers at the front line of rural community health care ("spokes"). Through regularly-scheduled live video sessions, ECHO creates a supportive community network where the spokes connect with the hub to discuss a) best practices in care and b) complex cases managed within their practice.[8] Two recent systematic reviews concluded that the ECHO Model is an effective and potentially cost-saving model that increases participant knowledge and patient access to quality care in remote and underserved locations.[9-10] We propose to test the effectiveness of two HPV vaccine communication interventions delivered through project ECHO at Penn State College of Medicine: an ECHO-delivered Announcement Approach training (HPV ECHO) and HPV ECHO plus systems follow-up communication for parents who initially decline vaccination (HPV ECHO+).

2.2 Previous Data

As part of a multi-state RCT with 148 high-volume primary care clinics, Dr. Calo (PI) led a study comparing in-person and live-webinar (an ECHO-like intervention) modalities to deliver HPV vaccination quality improvement coaching on HPV vaccination intermediate outcomes.[11] In both arms, coaching improved intermediate outcomes related to providers' knowledge and self-efficacy to improve HPV vaccine delivery (all $p<.05$). Providers also rated coaching sessions in the two arms equally highly on acceptability and satisfaction. Delivery cost per clinic for webinar coaching was two-thirds the cost for in-person coaching. These data, from an ECHO-like intervention, strongly suggest that the ECHO Model will be an efficient, acceptable, and economically feasible solution for delivering HPV vaccination best practices to rural clinics. This RCT study will be the first to rigorously evaluate two ECHO-delivered communication interventions on both HPV vaccination and implementation outcomes.

2.3 Study Rationale

The rationale for the project is that ECHO is a robust, highly-accessible platform to deliver best-practice communication interventions to rural providers and address the context-specific needs of their patients.

In our study, ECHO will allow us to make use of the Announcement Approach training's strengths while addressing its shortcomings. We will "grow" the Announcement Approach training by having an interdisciplinary team of experts offering an expanded best-practice curriculum that includes systems strategies to supplement provider communication, through a series of live videoconference sessions. The ECHO Model will also allow providers to discuss their own cases of vaccine hesitancy and seek solutions that are responsive to their patients' sociocultural and communication needs. We will also provide tailored visual aids to reduce the communication burden of providers and parents during (infographic cards) and after (recall notices) healthcare visits. With 218 ECHO hubs in 48 U.S. states, our project can exponentially increase national capacity to deliver HPV vaccination best practices across the country.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria for Primary Care Clinics

Family medicine or pediatric clinic in Pennsylvania
Having at least 100 active patients, ages 11-14
Access to computer or electronic device

Inclusion Criteria for Clinic Staff

Age: ≥18 years
Fluent in written and spoken English
Employed by primary care clinic in Pennsylvania
Involved in vaccine administration, communication, or scheduling

Inclusion Criteria for Parents in Nested Study

Age: ≥18 years
Fluent in written and spoken English
Parent/guardian of an adolescent ages 11–17, male or female
Declined initiation of HPV vaccine
Adolescent children must be a patient in a primary care clinic enrolled in study
Access to computer or electronic device

3.2 Exclusion Criteria for Primary Care Clinics

Primary care clinic outside of Pennsylvania
Participated in HPV vaccine communication or quality improvement research either through Penn State or another institution in the last 12 months

Exclusion Criteria for Individuals

Not fluent in written and spoken English
Decisional impairment
Not employed by a primary care clinic in PA
Not involved in vaccine administration, communication, or scheduling

Exclusion Criteria for Parents in Nested Study

Age: <18 years
Not fluent in written and spoken English
Not the parent/guardian of an adolescent ages 11–17
Adolescent already initiated HPV vaccination
Lack access to computer or electronic device

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Participants may voluntarily withdraw from the study at any time.

If a clinic staff participant leaves the clinic, they will be removed from the study, but another eligible staff from the clinic may fill in. Because the material learned through participation in the two interventions is meant to be communicated to other staff in the clinic or incorporated into clinic's routine practice, the site will not be removed from the study if they are able to find a replacement staff member.

For the nested study, subjects who choose to withdraw will be replaced by another identified potential participant from the same clinic.

3.3.2 Follow-up for withdrawn subjects

There will be no follow-up with any participants (i.e., clinics, clinic staff, parents in nested study) who choose to withdraw.

4.0 Recruitment Methods

4.1 Identification of subjects

The study will enroll 45 primary care clinics in Pennsylvania. Each primary care clinic enrolled in the study will be encouraged to invite up to 6 staff to participate in study activities (6 staff x 45 clinics = 270 staff). Clinic staff include physicians, clinic director or administrator, nurses, physician assistants, other healthcare professionals, and other staff involved in the administration, communication or scheduling of vaccines. Clinic recruitment will be facilitated through Penn State Health, the Southcentral Pennsylvania AHEC (Area Health Education Centers), and the Pennsylvania Association of Community Health Centers (PACHC). These three organizations have a combined membership of over 350 primary care clinics that might be eligible for this RCT. We do not have direct access to all providers within these clinics, so an email, flyer, or mailing will be sent to the clinic office manager, who will share the information with all providers in the clinic who can then choose to enroll and participate.

For the nested study, potential participants will be identified by clinic staff. Using the clinic's EHR (e.g., PowerChart), clinic staff will query the HPV vaccination status of adolescent patients ages 11-17 to identify those who have not yet started the first dose of the HPV vaccine and whose parents declined vaccination as indicated by provider notes.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

Primary care clinics will be recruited through collaborations with our stakeholder organizations, including Penn State Health, the Southcentral Pennsylvania AHEC, and PACHC through email communications and phone calls. These organizations have agreed, by providing letters of support, to partner with the study team to help with recruitment of primary care clinics. We will 1) provide study information to their leadership who can relay this information to their member clinics or 2) have our study team contacting the clinic director or lead staff ("clinic contact"). An email describing the study with a link to a screening form to determine eligibility will be sent to that clinic contact. We will also create a marketing website that provides study information and links clinics directly to the study screener and the research team's contact information.

The clinic director or lead staff will be asked to complete a brief screening form in REDCap if interested in participating in the study to ensure the clinic is eligible per criteria in section 3.0 of this protocol. Our study team will review screening forms to determine clinic eligibility. Those clinics screened eligible for participation in the RCT will be prompted with an online consent form and registration form to be completed by the clinic director or lead staff. After completion of these forms, study staff will enroll and randomize clinics to study arms. Study staff will then send an email communication to each clinic contact indicating which group they have been enrolled in. The clinic director or lead staff will be tasked with informing clinic staff about the study opportunity, and providing the contact information of the staff (up to 6 per clinic) who are interested in participating in study activities. Participating providers who enroll in the study through their clinic will then be invited to participate in a brief 30-minute key informant interview via email. Only the 1-2 providers most active participants (attended the most HPV ECHO training sessions) from each clinic will be invited to partake in the interview.

For the nested study, potential participants will be recruited via patient portal and email communications. After initial identification in the clinic's EHR, clinic staff collaborating with the research team will send the study flyer to potential subjects via the patient portal. However, this method has its faults as only 25% of parents of adolescents utilize the portal (preliminary data from two Penn State Health-affiliated primary care clinics). To overcome this barrier, we will send the study flyer to the email of potential participants who do not have an active patient portal. The email information will be retrieved by the clinic staff as available in the clinic's EHR. The flyer will have a link to connect interested parents to our secure REDCap system where parents will find screener questions to confirm eligibly, consent information, and additional information about the study. Parents who do not respond to our initial communication will be followed up with up to two additional email or patient portal communications.

4.2.2 Where potential subjects will be recruited.

Clinic recruitment will take place remotely via email, phone call, or virtual meetings to discuss specifics related to participation.
For the nested study, parents will be recruited using a study flyer to be sent via email or the patient portal. Phone or virtual calls to discuss specifics related to study participation will be available to potential participants per request. All potential subjects will be recruited from clinics assigned to the intervention groups.

4.2.3 When potential subjects will be recruited.

Clinics will be recruited from January 2021 to May 2023 in three annual waves (15 clinics in 2021; 15 clinics in 2022; and 15 clinics in 2023). Parents in the nested study will be recruited from August 2021 to December 2022 (enrolled parents will complete 5 total surveys over a one-year period, meaning they may be participating until December 2023).

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Eligibility will be determined via REDCap screening form. Staff employed by the clinic will not be identified until the clinic has been enrolled in the study. Inclusion/exclusion criteria is based

upon primary care clinic characteristics. There will be an explanation of the study, including time commitment and description of the study, but consent will not take place until after screening.

For the nested study, the screening process will begin before obtaining informed consent with an electronic pre-screening by a clinic staff. Prior to being asked to participate in the study and obtaining informed consent, clinic staff will query the clinic's EHR to identify adolescent patients ages 11-17 who have not yet started the first dose of the HPV vaccine and whose parents declined vaccination as indicated by provider notes. Vaccine declination must occur during the time the clinic is enrolled in the study. Once a potential participant is identified to meet the inclusion criteria, these subjects will receive a study invitation via email or patient portal. They will be presented with the SER to inform them of the study requirements so that they may choose to consent to participate in the study according to the procedures described. Participants will give implied consent by completing a screener form in REDCap in order to enroll and participate in this study. Screening will be done electronically through REDCap.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☐ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **<u>Exempt Research at all Locations Except Penn State Health and the College of Medicine</u>: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312-Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):**

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the records that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Clinic sites will be recruited and their explicit permission to recruit their employees will be documented. As part of the permission, clinic sites will provide a list of up to 6 clinic staff and their emails that are interested in participating in the study. After we receive the name and email of interested clinic staff, they will receive an email invite to connect them to the REDCap with the SER and baseline survey. To ensure interest, participants will be asked independent of their clinic director/lead if they are willing and able to participate. Their responses will not be shared with the clinic director/lead. Completion of the baseline survey serves as their implied consent (no screener). Participants who are invited and interested in participating in the key informant interview will be presented with an online SER prior to the interview and will give their implied consent prior to the scheduled interview.

The consent process for parents in the nested study will occur at the beginning of the eligibility screener in REDCap where potential participants will be prompted with the SER document content. Once participant reviews the SER, they will complete the screener, which serves as their implied consent.

5.2.2 Coercion or Undue Influence during Consent

All participants, including those in the nested study, will be prompted with the following text prior to start any survey or study activity: "Your participation is voluntary and you do not have to answer any questions that you do not want to answer." The SER also informs subjects that their participation is voluntary.

5.3 Waiver of Written Documentation of Consent

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more

than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Participants will give implied consent. Their completion of the baseline survey (clinic staff) or the eligibility screener (parents in nested study) after reviewing the SER indicates their consent to participate in the study.

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

The SER will be placed at the beginning of the baseline survey for clinic staff. Clinic staff that also participate in the interviews will be preented with another SER at the beginning of a brief questionnaire that confirms their willingness to participate and availability for scheduling the interview. For the nested study, potential participants will receive the SER prior to completing the screener.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

5.4.1 Indicate the elements of informed consent to be omitted or altered

N/A

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

N/A

5.4.3 Describe why the research involves no more than minimal risk to subjects.

N/A

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.4.6 Debriefing

N/A

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.5.5 Additional pertinent information after participation

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Non-English speaking is an exclusion criterion.

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

N/A

5.6.2.2 Adults Unable To Consent

N/A

5.6.2.3 Assent of Adults Unable to Consent

N/A

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.2.1 Parental Permission

Parental permission is addressed within the SER. By completing the screener parents are providing their implied consent for their child's PHI (HPV vaccine uptake status) information to be used as part of this research study.

5.6.2.2 Assent of subjects who are not yet adults

A waiver of child assent is requested for this study. Children have no active role in study activities. Parents are fully informed of and they will complete all study activities. Also, as usual care, parents will be the ones providing permission during the child's appointment regarding administration of the HPV vaccine.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☐ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

All identifiers will be destroyed when the study ends.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

For the nested study, using PHI from clinics' EHR is the only way to identify potential subjects whose children have not yet started HPV vaccination. Assigned clinic staff will access these data to review eligibility criteria and send electronic flyer to invite those subjects to participate in the study. All other study vaccine data will be received from the clinics aggregated at the clinic level.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The study's primary outcome measure and most secondary measures require the use of EHR data from participating clinics that contain some PHI. However, these data will be received aggregated at the clinic level so getting consent from each patient is impractical because we will not obtain individual-level PHI.

For clinic staff an alteration is requested as the study is conducted virtually and is minimal risk. Clinic staff will still be presented with the SER prior to completing the baseline survey. Completion of the baseline survey serves as their implied consent to participate in the study.

For the nested study, in order to identify potential participants for recruitment, there is a need to access a limited set of PHI. Clinic staff will access patients' EHR for the purpose of confirming patient gender, age, and HPV immunization status before screening the patients' parents and obtain parental consent. Parent emails will be obtained to distribute our recruitment flyer. A partial waiver is requested for recruitment purposes only. We will only use the waiver for authorization to the PHI for the recruitment process. Eligible patients will give their implied consent, if they refuse to participate in the study, we will no longer use their PHI.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other

permitted uses and disclosures according to federal regulations. The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations. Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

We will conduct a cluster randomized controlled trial to assess the impact of two ECHO-delivered HPV vaccine communication interventions on HPV vaccine initiation in primary care clinics. Using a 3-arm design, 45 rural clinics will be randomized in 3 waves (15 clinics per wave) to receive: ECHO-delivered Announcement Approach training (HPV ECHO); HPV ECHO plus systems communication (HPV ECHO+); or control. Participating clinic staff will be asked to enroll in the 8-session curriculum (only HPV ECHO and HPV ECHO+ arms) and complete two online surveys (all arms). Active clinic staff that were randomized to the intervention arms will be invited to participate in a brief 30-minute interview. The study includes a nested study with a subset of 211 parents to evaluate the impact of vaccine information on secondary acceptance of HPV vaccination. All study activities will be completed by participates using their small media devices like tablets, desktop or laptop computers, and smart phones.

7.2 Study Procedures

7.2.1 Registration/Baseline Survey – Intervention groups and control

Prior to the start of the study, all participants will be asked questions about their knowledge, attitude, confidence, and skills regarding HPV vaccination and vaccine communication practices. In addition, participants will be asked general information such as academic credentials, years of experience, and role in primary care clinic.
Please note the baseline survey, case presentation, and final evalutation surveys are used regularly in ECHO series that are IRB approved under CATS study ID #10821.
As part of the baseline survey the clinic's study contact will enter in the immunization data for the participating clinic site, these measures are part of our primary outcome.

7.2.2 Case Presentation – HPV ECHO and HPV ECHO+ Intervention Groups

Case presentation information will be collected prior to each teleECHO clinic session from participants in the intervention via REDCap. No patient level data will be collected. Case template forms will collect de-identified data on specific patient cases about vaccine hesitancy that will be used in case-based learning opportunities.

Please note, this is not a data collection form but used as part of the ECHO educational model to drive discussion and information sharing. More information for use of the case forms and the ECHO Model can be found under CATS study ID #10821.

7.2.3 Curriculum – HPV ECHO and HPV ECHO+ Intervention Groups

HPV ECHO intervention arm (please note that information regarding specifics of ECHO clinics may be found in CATS Study 10281): Clinics in this arm will receive the intervention via real-time, interactive videoconferencing using Zoom, a user-friendly, HIPAA-compliant, cloud-based software application offered at no cost to participants. Sessions will be held twice a month for 4 months (8 sessions total) at regularly scheduled times (e.g., every 2nd and 4th Wednesday from

1:00–2:00 PM) convenient to providers. Sessions will last 60 minutes each and will share the following format (the number, frequency and length of sessions are usual for the ECHO Model[8]):

- *Introductions* (5 minutes) – Introductions are intended to provide an inviting atmosphere to hub and spoke participants. A full roster and contact information of providers and hub experts will also be provided to facilitate networking outside of ECHO sessions.
- *Didactic presentations* (20 minutes) – Experts will deliver a short PowerPoint presentation with question and answer session on the topic. Presentations and session materials will be available to participants through our online resource library in Penn State Box, a no-cost, cloud storage and collaboration system.
- *Case presentations* (30 minutes) – Each session includes case-based discussions to ensure mastery of the content and skills. Each spoke provider will present at least one case during the program. In the assigned session, spoke providers will spend 5 minutes presenting a de-identified case for one of their current adolescent patients. Other spoke providers are encouraged to ask clarifying questions and weigh in on recommendations, then the hub experts provide advice on how to address each case using best practices. We will discuss two cases per session. To protect patient confidentiality, cases are presented in a de-identified manner, without disclosure of PHI. There are instructions for presenting a case shared with participants prior to the start of the ECHO series in the Welcome Guide. This welcome guide is provided to all ECHO participants and describes the use of zoom, how to present a case, and provides introductions to the hub team. An assigned, confidential ECHO ID# is used to identify presented cases in the order in which they are received. The ECHO ID is used to match case presentation material from REDCap to the session in which it was presented. If PHI or identifiers are included, they are removed in REDCap prior to sharing with participants. Prior to a session, all pertinent information for each patient is entered into a standardized REDCap case form by the presenting provider. The hub will then generate a case presentation page which is screen-shared during session. Best-practice recommendations will be summarized verbally at the conclusion of each case presentation and forwarded by email to all spoke providers.
- *Close and debrief* (5 minutes) – All sessions conclude with a reminder to complete the session evaluation, and the hub team encouraging providers to put into practice what they have learned.

All clinics assigned to this arm will participate together during an ECHO session, which encourages discussion. All sessions will be recorded. Session topics will focus on training providers to use the Announcement Approach to communicate HPV vaccination to parents, as well as evidence-based systems strategies they can use to supplement and sustain their communication efforts. The curriculum will orient providers with the latest data about HPV-related cancers and vaccination rates, ACIP guidelines, HPV vaccine effectiveness and safety, the rationale for targeting younger adolescents, and to consistently deliver strong recommendations (Session 1 [S1]). Even though participants may be familiar with this material, the hub team will begin to gain providers' trust by illustrating their expertise and interest in HPV vaccination. In the next sessions, experts will train providers on how to: use a structured approach and research-tested messages for answering common parent questions and concerns (S2 and S3), and engage in conversations with vaccine-hesitant parents (S4). Providers will then receive presentations on systems strategies including how to: conduct immunization quality improvement (S5), engage all clinic personnel in vaccination efforts (S6), and access evidence-based materials and community resources (S7). We will finish discussing how providers can use reminder and recall notices and sustain HPV vaccination efforts (S8).

HPV ECHO+ intervention arm. Clinics in this study arm will receive HPV ECHO sessions, as described above, plus systems communications to parents who initially decline vaccination. Sessions for intervention arms will be identical in format and curriculum. Case presentations will

be unique to each arm as spoke providers will present and discuss their unique clinical challenges related to HPV vaccination. We do not anticipate sessions to diverge across arms because cases will address common topics seen in clinics.

For our systems communication, following, standard practice, participating clinics will prospectively identify patients and parents who forgo HPV vaccination at healthcare visits and will send recall notices to notify parents that their child is behind for HPV vaccination and address their primary reason for not vaccinating. We selected recall notices as our systems strategy because studies indicate that they can be delivered through various modalities and be equally effective.[12-16] Importantly, most EHR programs are capable of creating reports that identify specific populations (i.e., children whose parents declined HPV vaccination) for recall notices.[17] Also, most EHR programs can be programmed to send automatic recall notices that are tailored for patients and accompanied by educational messages.[17] Our systems strategy will take advantage of those features available in most EHR programs. As providers will be trained to ask and document the parent's main concern about HPV vaccination (a step in the Announcement Approach), recall notices will include research-tested messages to specifically address the reported concern. Following best practices, our recall notices will use announcement-style language, state that the provider strongly recommends that the child receive the vaccine now, emphasize cancer prevention, and encourage early vaccination to take advantage of the 2-dose schedule. When available, these communications will also point out the convenience of nurse visits. Notices will go out at the beginning of each calendar month. Clinics will send secure electronic notices to parents through the patient's EHR portal as the primary communication modality. Clinics will send mailed recall notices to parents who have opted out of the portal messaging, these will be provided by study. Regardless of the modality, notices will look similar. Recall notices will be sent to vaccine declining parents every 6 months for 12 consecutive months starting the sixth month after the start of the intervention (6- and 12-month). These communications would end early if the adolescent initiated HPV vaccination within the 12 months or the parent declined receiving these recall notices.

7.2.4 Wait List Control Group

Participants in this arm will not receive any HPV ECHO intervention during the study period. After the intervention training and outcome evaluations have been completed (12 months), clinics in the control group will have full access to the recorded HPV ECHO sessions (intervention programming) and study materials (e.g., electronic recall notices). To keep the control group engaged, control participants will be invited to participate in other active ECHO sessions that are relevant to primary care, but do not overlap with vaccination. Control group participants will be able to receive no-cost CME credits for attending these live ECHO sessions.

7.2.5 Quarterly Check-ins – Intervention and Control Group

All participants in the intervention and control groups will complete 4 quarterly check-ins to remind them about their participation in the study and assess if the clinic has engaged in any other vaccine communication or quality improvement training or project (4 questions).

7.2.6 Final Evaluation – Intervention and Control Group

All participants in the intervention (HPV ECHO and HPV ECHO+) and control groups will complete a final evaluation at 4-months at the completion of the telementoring sessions. The final evaluation will repeat measures from baseline. This evaluation will take you approximately 15-20 minutes to complete. As part of the final evaluation, at 12-months, the clinic's study contact will enter in the immunization data for the participating clinic site (repeated measures from the baseline).

7.2.7 Key Informant Interviews

One or two of the most active participants (attended the most HPV ECHO live sessions) from each intervention clinic (HPV ECHO and HPV ECHO+) will be invited to participate in a 30-minute interview. The interview will occur after participants complete the series and final evaluation. Interviews will occur virtually via Zoom and will be audio and video recorded.

7.2.8 Nested study

In the exploratory nested study, a total of 211 parents of adolescents, ages 11 to 17, will be recruited over a 2-year period and will be followed for up to 12 months. Parents will be eligible if they decline the first dose of HPV vaccination for their child after receiving a provider recommendation and the provider documents the main reason for declining vaccination in the child's EHR. We will target parents whose children have received at least one of the other vaccines recommended for adolescents (Tdap or meningococcal) because they have already shown some positive attitude towards vaccination and may be more amenable to getting the HPV vaccine at a later visit than those who completely oppose all vaccines. HPV vaccine uptake will be tracked using the child's EHR.

Recruitment of parents will take place in a subset of 4 PennState Health clinics (~50 parents per clinic). Our project manager will train clinic's nurses or staff on the study protocol, and they will identify eligible subjects who will receive an invitation to complete screener and consent. Parents will complete a total of 5 online surveys through our secure, web-based REDCap platform at baseline (within the first week of declining HPV vaccination) and then, every 3 months for 12 months (3-, 6-, 9- and 12-month follow-ups). Parents will receive follow-up surveys 7 days after the recall notices (HPV ECHO+ arm; Aim 1) so they would have enough time to make an appointment or get the vaccine. For each survey, we will send up to two email or mail reminders to non-respondents. If the parent gets the HPV vaccine for their child within the first few months of study enrollment, they will continue to receive all 5 surveys. The HPV vaccine is a multi-dose vaccine, so assessing vaccine communication over the 12-month time period will provide more information on vaccine initiation and completion.

7.3 Duration of Participation

Duration of participation for primary clinic staff, regardless of study arm assignment, includes 15-20 minutes for the baseline and 15-20 minutes for the follow-up survey. In addition, participants in HPV ECHO and HPV ECHO+, will participate in 8 hours of intervention training, and may complete up to eight 5-minute surveys if they are interested in obtaining continuing education credits. Preparation for case discussions in the two intervention groups will take approximately 2 hours. A subset of clinic staff may also choose to participate in the key informant interviews. The interviews will last 30 minutes. Total participation will span a period of 6 months.
For the nested study, duration of participation is 15 minutes per online survey (5 in total) through a 12-month period.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We will recruit 45 primary care clinics in Pennsylvania, and each participating clinic can bring up to 6 staff to participate in the study, including physicians, nurses, physician assistants, medical director and other staff involved in the delivery, communication or scheduling of vaccine (n=270). Of those clinic staff, only 1-2 per intervention clinic will be invited to participate (n=60).

For the nested study, we will recruit a total of 211 parents of adolescents, ages 11 to 17. Of note, we have recruited 211 parents following the recruitment procedures outlined in this protocol. The final invite was sent in September 2023 and the final participant chose to enrol in November 2023.

8.2 Sample size determination

This study will include 45 clinics with 15 randomized to each of the 3 arms. Monte Carlo simulations were used to estimate power under the following assumptions: vaccine initiation rate of 40% in the control arm, a mean of 425 adolescents/clinic (ages 11-14), and a between-clinic standard deviation of 0.05. Based on these simulations, we estimate that this study design will yield statistical power of at least 0.90, with a one-sided Type 1 error of 0.025, to detect a 5% increase in the proportion of adolescents who have initiated HPV vaccination (≥1 dose) in intervention versus control group (H1). The 0.025 level uses Bonferroni correction to adjust for the two comparisons to be performed (HPV ECHO versus control and HPV ECHO+ versus control). The expected number of adolescents/clinic and vaccine initiation rate were estimated from available data of a sample of 15 primary care clinics from Penn State Health.

For the key informant interviews, we will conduct rapid qualitative analyses after each cohort and will adjust the sample size based on when we reach data saturation.

The nested study is exploratory; it does not include a sample size determination.

8.3 Statistical methods

8.3.1. Randomization

Using a 1:1:1 ratio, we will randomly assign clinics to receive either HPV ECHO, HPV ECHO+, or control. Each arm will have 15 clinics, for a total of 45 clinics. Covariate-constrained randomization will be used to ensure balance among the three arms with respect to clinic size, clinic type (academic vs. non-academic), rurality/urbanicity using Rural-Urban Continuum Codes from clinic's physical address (RUCC), and historic adolescent HPV vaccination rates. Given a core component of the ECHO Model is spoke provider presentations of cases, sessions are usually capped to 25 participants to allow each provider to present at least once during the program and actively engage in discussions. In our prior RCT of ECHO-alike quality improvement coaching, an average of 5 providers per clinic attended live webinars.[11] Accordingly, we will have three waves of 15 clinics each (one wave per year during years 2 to 4) and will randomize them to the 3 study arms (5 clinics per arm, per wave); this design will maximize accommodation of participants in ECHO sessions. Randomization will ensure groups are balanced among the waves.

8.3.2. Effectiveness of ECHO

Our primary outcome is the proportion of patients, ages 11-14, who have initiated their HPV vaccination (≥1 dose) in the 12 months after ECHO implementation. We target 11- to 14-year-olds versus older adolescents because revised ACIP guidelines may motivate more parents to initiate the 2-dose series at younger ages to take advantage of the reduced vaccine schedule. We also target initiation versus completion because it is a more amenable indicator of changes in providers' practices. Our secondary outcomes include vaccination by gender, for 15-17-year-olds, up-to-date HPV vaccination, for concomitant vaccination (i.e., with Tdap and meningococcal vaccines), and at interim time points (3-, 6-, and 9-month follow-up). We will assess Aim 1 outcomes using provider-verified EHR data from participating clinics. We will use EHR data because adoption and use of EHR for documenting vaccinations in Pennsylvania is very high; contrary to vaccination reporting to the state Immunization Information System (IIS), which is voluntary for adolescent vaccines (low IIS capacity) as the majority of U.S. states.[18]

We will also characterize clinics by size (total number of adolescent patients), patient insurance mix (proportion of VFC-eligible adolescents), specialty (pediatrics or family medicine), rurality (RUCC), HPV vaccination at baseline, and patient demographics (proportion by sex, race/ethnicity). Our experienced biostatistician will work with each participating provider or their clinic's data manager to ensure that EHR queries follow American Immunization Registry Association's guidelines to properly define study populations and vaccination status.[19] All these data will be aggregated at the clinic level, we will not request nor receive any patient-level data.

For the primary outcome, data will be analyzed using a generalized linear mixed-effects model with a binomial distribution and logit link. The model will include treatment group as a fixed effect, and wave and clinic as random effects. Contrasts will be constructed to test HPV ECHO versus control and HPV ECHO+ versus control. Analyses for secondary outcomes will be performed using the same model specified for the primary outcome, as well as respective contrasts. For analysis by sex, multiplicative interaction terms for sex by treatment will be added to the model.

8.3.3. Implementation outcomes

Our evaluation of implementation outcomes is informed by both the Damschroder's Consolidated Framework for Implementation Research (CFIR)[20] and Proctor's Implementation Outcomes Framework (IOF)[21] and will allow us to capture the complexity of implementation in a variety of clinics within their unique contexts. Data collection will be done through the following activities: 1) Implementation surveys will be administered online through REDCap to clinic staff from enrolled clinics. The surveys will evaluate appropriateness and acceptability using adapted items from the Intervention Appropriateness Measure and the Acceptability of Intervention Measure scales.[22] The survey will also evaluate adoption using items from validated instruments measuring the frequency and quality of HPV vaccine recommendations and adherence to the Announcement Approach steps. 2) Fidelity checklists will be used to document fidelity or the extent to which hub experts (e.g., session format, length) and participants (e.g., case discussion) participate in ECHO sessions per protocol. With the permission of ECHO participants, we will video-record and watch one-third of sessions for internal quality improvement. 3) Key informant interviews will be conducted with active clinic staff that are enrolled in the intervention clinics. The interview will evaluate the acceptability of the training using some CFIR measures, and evaluate the adoption of measures into practice. These will be conducted after each cohort to determine if adaptations to the intervention need to be made to the intervention. 4) Recruitment tracking to assess reach to clinics and providers including attendance at each session. For clinics that decline participation, we will document the reason. 5) Costs will be estimated from the perspective of providers.[23] For both intervention arms and control group, we will calculate the incremental costs as: (i) any new technology the providers needed to purchase to participate in sessions, (ii) providers' time to participate in sessions, including time to compile case information (costs estimated as the number of hours for each provider type multiplied by an average hourly wage from the Bureau of Labor Statistics), and (iii) hub staff time calculated similarly to (ii). While hub staff time are not paid by each clinic site, we include these costs as representative of incremental costs that would need to be considered in future expansions. For the HPV ECHO+ incremental costs, we will also include: (iv) any new technology that needs to be purchased to enable communication to parents and (v) additional provider or clinic staff time to facilitate the delivery of these communications.

8.3.4. Nested study

All surveys will systematically assess exposure to and impact of vaccine information from study arms or naturally-occurring sources (i.e., social media, traditional media, social networks). We will assess HPV vaccination intentions using a 3-item scale that addresses the three aspects of intentions (i.e., expectation, desire, and planning).[24] We will also assess overall HPV vaccination attitudes and beliefs using a short validated scale.[25] We will also ask parents whether the study communication was adequate to address their main concern, whether external information impacted their main concern, and whether their main concern changed over time.[26] We will assess information's transport and credibility using validated scales conceptualized in narrative persuasion theories.[27-28] Exploratory analyses will focus on describing the exposure to vaccine information, as well as its impact on attitudes and secondary acceptance of HPV vaccination among the subset of parents surveyed. Specifically, we will conduct mediation analyses to explore the constructs that could explain our hypothesis; why HPV ECHO+ is associated with greater secondary acceptance than HPV ECHO. We will calculate the indirect effects based on standardized path coefficients and conduct bootstrapping.

9.0 Data and Safety Monitoring Plan

Not applicable: This study does not involve more than minimal risk to subjects, and the magnitude of harm/discomfort is not greater than that ordinarily encountered in daily life.

9.1 Periodic evaluation of data

N/A

9.2 Data that are reviewed

N/A

9.3 Method of collection of safety information

N/A

9.4 Frequency of data collection

N/A

9.5 Individuals reviewing the data

N/A

9.6 Frequency of review of cumulative data

N/A

9.7 Statistical tests

N/A

9.8 Suspension of research

N/A

10.0 Risks

The risk of participating is minimal, and the magnitude of harm/discomfort is not greater than that ordinarily encountered in daily life. In the HPV ECHO+ group and the nested study, the recall notices to be used do not contain any graphic or explicit content but may invoke an emotional response due to the nature of the topic (i.e., vaccination). However, these are health topics commonly discussed in primary care visits, and recall notices are standard practice. The questions asked in the surveys are not sensitive in nature and come from validated instruments used in prior studies.

There is a risk of loss of confidentiality if participant information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of participants' electronic data will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed. Personal information and survey responses will be labeled with a participant code assigned by REDCap and stored in this database. All HPV ECHO sessions will be recorded, session recordings will only be available to clinic staff that are enrolled in the study. Employers will not have access to the recordings.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

There are no direct benefits to participants. However, primary care clinics may include improved rates of HPV vaccination. Potential benefits to clinic staff may include improvement in confidence, self-efficacy,

knowledge, and skills to communicate about HPV vaccination. Potential benefits to parents in the nested study may include their children getting the HPV vaccine.

11.2 Potential Benefits to Others

Benefits to others are long term, including improved patient care and may contribute to the dissemination if this type of training to help clinics communicate with parents about the importance of HPV vaccination and then, increase HPV vaccination rates.

12.0 Sharing Results with Subjects

For clinics and clinic staff participating in the study, a project brief will be created at the conclusion of the study that will be shared with clinics.
For the nested study, results will not be shared with participants.

13.0 Subject Payment and/or Travel Reimbursements

Clinic staff will receive monetary compensation for their participation in the study, but clinic staff will receive up to 8 no-cost CME credits. One CME credit will be awarded per each hour of participation. Clinics may also elect to receive MOC Part 4 credit for their clinic's participation in the intervention (25 points for general pediatrics, 20 points for family medicine). Providers will also receive a $50 gift card (Amazon or Target) for completing the baseline and follow-up surveys for up to $100 total. Additionally, providers that participate in the 30-minute key informant interview will be able to receive an additional $50 gift card as compensation for their time. This means that clinic staff that choose to participate in both the surveys and the interviews will be able to receive up to $150 for their participation. Clinics such as FQHCs have expressed concern over the financial burden caused by the lost clinic time due to their participation. To ensure all clinics have an equal opportunity to participate, funds have been made available for clinics to have the option to ask for compensation at $150/session attended for up to $1200/clinic, if the clinic has at least one attendant at each of the 8 sessions.

Participants in the nested study will receive a $25 gift card for each of the first four online survey they complete, and $50 for completing the final survey. In total, participants can be compensated up to $150 (5 surveys) for their participation in this study.

14.0 Economic Burden to Subjects

14.1 Costs

There are no financial costs associated with participating in this research.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

The ECHO model utilizes videconferencing technology (Zoom) as a platform for telementoring and case-based learning, with a hub-and-spoke structure. Participants may participate in the study from any location. For the

nested study, all study activities will occur at any locations chosen by participants because they can access the screener, SER, and surveys through their personal electronic devices.

15.2 Feasibility of recruiting the required number of subjects

We do not anticipate any challenges in recruiting, given the support of Penn State Health and the Pennsylvania Association of Community Health Centers to assist with recruitment activities. For the nested study, participants will be recruited with the support of four partnering clinics.

15.3 PI Time devoted to conducting the research

Dr. Calo will devote 25% to oversee study activities.

15.4 Availability of medical or psychological resources

It is not anticipated that medical or psychological resources will be needed, given that study procedures are minimal risk.

15.5 Process for informing Study Team

The investigators and project coordinator/study staff have completed their required Collaborative IRB Training Initiative (CITI) in the protection of human research subjects. The study team will be educated on the importance of confidentiality, and proper data handling and storage. Regular team meetings and emails will be used to coordinate the study.

16.0 Other Approvals

16.1 Other Approvals from External Entities

N/A

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

N/A

18.0 Adverse Event Reporting

18.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored

N/A

20.2 Location of storage
N/A

20.3 Duration of storage
N/A

20.4 Access to data and/or specimens
N/A

20.5 Procedures to release data or specimens
N/A

20.6 Process for returning results
N/A

21.0 References

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22.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form