Using Connected Health to Increase Lung Cancer Screening: Single Center Randomized Pilot Trial

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Protocol Summary

Title	Using Connected Health to Increase Lung Cancer Screening (CH-LCS)
Short Title	Increasing Lung Cancer Screening
Co-Principal Investigators	Katharine Rendle, PhD, MSW, MPH Anil Vachani, MD, MS
Co-Investigators	
Design	Prospective, randomized controlled trial
Objectives	**Aim 1.** To pilot test the effect and feasibility of using direct outreach and telemedicine referral to increase lung cancer screening (LCS) counseling and uptake among screening-eligible patients. **Aim 2.** To explore the moderating effects of individual and cognitive moderators (patient characteristics, risk factors, and psychological beliefs) on LCS screening intention and uptake.
Trial Duration	1.5 years
Study Sites	The University of Pennsylvania Health System
Sample Size	Approximately 600 patients
Patient Eligibility	Aged 55-77 Had a primary care visit at UPHS within the last 24 months Never had a low-dose CT for lung cancer screening Heavy smokers (30+ pack year and current smoker or quit within 15 years) Access to phone and internet English-speaking Have an assigned primary care provider at UPHS (excluding Lancaster General and Princeton) No history of lung cancer

Interventions	1) Following enrollment, all patients will be asked to complete a brief baseline survey assessing demographics, smokingand LCS cancer beliefs, and screening intention using measures previously applied in other studies, and will receive $20 upon completion. 2) Following completion of the baseline survey, patients will be randomized into one of the two treatment arms. All patients will receive brief information on lung cancer screening risks and benefits adapted from validated decision support tool. Following survey completion: a) Patients in the usual care arm will be provided with contact information for the Penn LCS Program and encouraged to discuss LCS with their providers and b) Patients in the intervention arm will be offered to be directly referred to the LCS telemedicine program and asked for their permission to provide their phone number to the Penn LCS navigator. 3) All patients will be re-contacted approximately 6-8 weeks after enrollment to conduct a brief survey assessing decision-making, quality of shared decision-making and telehealth visit (if completed). Patients will receive an additional $10 upon final survey completion.
Outcomes	**Primary Outcome:** Completion of LCS counseling, defined by completion of a telemedicine visit, in-person counseling visit (CPT G0296), or documentation of counseling in EHR provider notes. **Secondary Outcome:** Completion of LDCT scan for LCS **Exploratory Outcomes**: Decisional conflict and screening preferences Quality of shared decision making and telehealth visit Referral to smoking cessation program
Primary Analysis	• Intention-to-treat (ITT) analyses using logistic regression to assess the overall effect of the intervention on completion of LCS counseling.
Secondary Analyses	• Baseline survey and clinical data will be used to explore potential predictors (demographics, belief and cognitive biases, and other factors) on screening intention and LCS uptake. We will fit multivariable regression models with intervention, moderator, and interaction terms to assess effect modification based on significance of the interaction term.
Study Oversight	• Trial oversight will be conducted by the University of Pennsylvania Institutional Review Board. • Safety will be monitored on an ongoing basis by the co-PIs and study team.

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1. Background and Rationale

Recommendations for annual lung cancer screening (LCS) are largely based on the results of the National Lung Screening Trial (NLST) that found a 20% reduction in lung-cancer specific mortality with annual low-dose computed tomography (LDCT) in comparison to chest radiography (1-2). In addition to potential benefits, substantial harms are linked to LCS including high rates of false positives, radiation exposure, and surgical complications (3). Based on this evidence, in 2013, the United States Preventive Services Task Force (USPSTF) provided a Grade "B" recommendation for annual LCS for asymptomatic adults aged 55-80 who are or have been heavy smokers (≥30 pack-years of smoking and quit-date ≤ 15 years ago), and are able to undergo surgery (4). In 2015, The Centers for Medicare and Medicaid Services (CMS) issued national coverage for LCS requiring that LCS counseling, which must include shared decision-making and tobacco cessation counseling, occur prior to LCS (5). CMS also provides reimbursement for LCS counseling to further support providers to engage in meaningful, collaborative conversations about LCS with patients (6, 7). Despite widespread support, uptake and implementation of LCS across the United States has been low (estimated 3-5% screening-eligible population screened) (8). Locally, since the onset of the Penn Medicine LCS Program in 2014, over 3,500 individual patients have received LCS; however, documentation and reimbursement of LCS counseling (under CPT G0297) is very low.

Challenges of implementing LCS include substantial barriers to identifying screening-eligible patients, supporting high-quality decision-making, and remaining uncertainties regarding risks and benefits (9,10). For other types of cancer screening, insights from behavioral economics have been applied to understand how cognitive biases impact screening uptake (11-13). Yet for LCS, there is limited to no evidence on how these biases effect screening behaviors (14). Given the complexities of LCS, in which the benefits do not clearly outweigh the harms, understanding how these biases impact screening can help inform development of intervention strategies that both support informed decision-making and increase uptake among eligible patients. Leveraging the Penn LCS Program, and existing LCS database developed within our Penn Population Center of Excellence in Precision Lung Cancer Screening Project, we will combine insights from behavioral economics and connected health strategies to pilot test connected health approaches including telemedicine visits to improve frequency and quality of LCS counseling, and to explore cognitive moderators of LCS screening intention and uptake.

Results from this study will be used to develop tailored outreach and identify effective strategies for expanding our pilot study. We will seek R01-level funding to assess how proposed strategies and outreach impacts screening uptake across diverse populations. The long-term goal is to decrease lung cancer burden by increasing utilization of LCS and providing clinicians and patients with effective strategies to deliver high-quality, patient-centered care. This study will also advance scientific understanding of the mechanisms that drive or hinder health behavior in the context of cancer prevention.

2. Objectives

2.1. Specific Aims

The specific aims of this single-center pilot randomized trial are:

1. Pilot test the effect and feasibility of using direct outreach and telemedicine referral to increase LCS counseling and LCS uptake among screening-eligible patients.
2. Explore the moderating effects of individual and cognitive moderators (patient characteristics, risk factors, and psychological beliefs) on screening intention and uptake.

2.2. Primary Outcome

The primary outcome measure is completion of LCS counseling, defined by completion of a

telemedicine visit, in-person counseling visit (CPT G0296), or documentation of counseling in EHR provider notes.

2.3. Secondary Outcome
The secondary outcome is completion of LDCT scan for LCS.

2.4. Exploratory Outcomes
Exploratory outcomes include quality of decision making and telehealth visits (evaluated by patient survey) and referral to smoking cessation program (evaluated by EMR data).

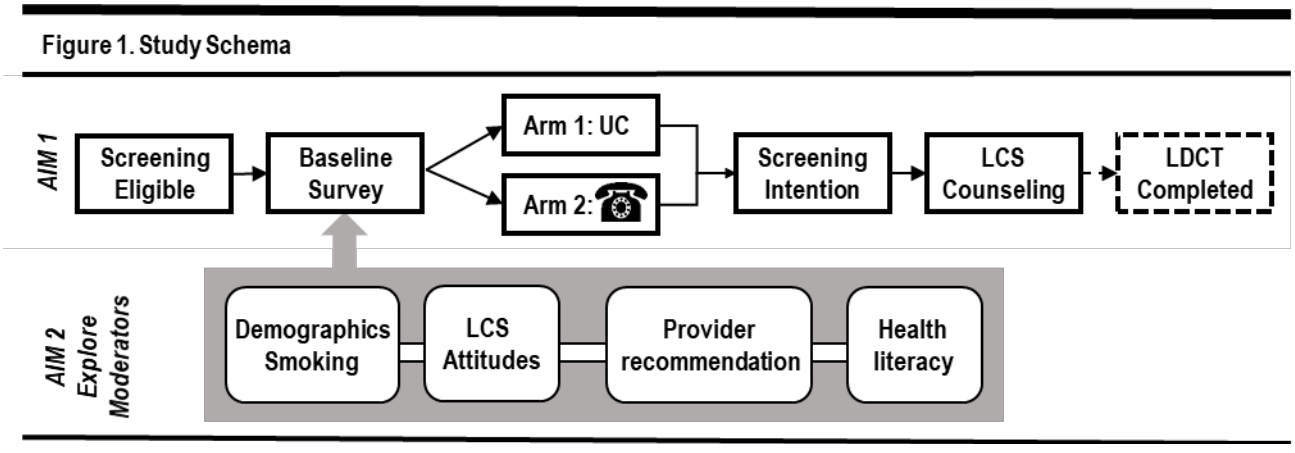
3. Study Design

3.1. Overview
This study will consist of two primary aims designed to help advance quality and utilization of LCS across our patient population. For Aim 1, we will first use routinely-collected medical record data to identify screening-eligible adults for LCS. All patients who meet the study population criteria will be invited to participate, but only those who confirm screening eligibility will be eligible to enroll. Patients who confirm eligibility and agree to participate will be randomized into two study arms: 1) usual care or 2) telemedicine LCS counseling referral. For Aim 2, each arm will first complete a baseline survey to explore how cognitive biases impact screening intention and uptake. Patients in both arms will also receive brief information on lung cancer screening using the validated AHRQ LCS decision tool, and asked to report screening knowledge and preferences before and after exposure to the information. All interventions will be administered using a secure, web-based platform (REDCap).

3.2. Study Setting
We will test the interventions among patients who meet LCS and study criteria in the outpatient setting within the University of Pennsylvania Health System (UPHS). We will not include patients who are receiving primary care at Princeton Health or Lancaster General.

3.3. Schema
This is a single center 2-arm prospective randomized controlled trial. Patients who meet eligibility and complete baseline survey will be randomized (1:1) to either usual care or treatment arm.

Figure 1. Study Schema



3.4. Accrual and Duration

To ensure our study is aligned with workflows of the Penn LCS Program, we will invite potentially eligible adults in randomly sampled, sequential batches (approximately four batches of 1,500 each for a total of 6,000 invited patients). Based on previous pragmatic trials (15), we anticipate that approximately 20% of these patients will respond to the invitation. Of these estimated 1,200 adults, we anticipate that 50% will meet screening criteria and will enroll into the study, resulting in an estimated sample size of 600. After each batch, we will assess and adapt as needed to reach the sample size and to align with clinical capacity.

3.5. Study Timeline

Project Timeline	2020			2021												2022	
		N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F
Study Preparation																	
Finalize study materials	•	•	•														
Refine telehealth workflow	•	•	•														
IRB & staff training	•	•	•														
Trial Activities																	
Invite & Enroll				B1	B1		B2	B2		B3	B3		B4	B4			
LCS Counseling Visits					B1	B1	B1	B2	B2	B2	B2	B3	B3	B4	B4	B4	
Rapid Assessment						B2			B3			B4					
Post-Survey Administration						B1	B1		B2	B2		B3	B3		B4	B4	
Data Ascertainment & Analysis		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•

3.6. Inclusion Criteria

All of the following patient inclusion criteria must be met:

1) Aged 55-77
2) Had a primary care visit at UPHS within the last 24 months
3) No history of lung cancer
4) Heavy smokers (30+ pack year and current smoker or quit within 15 years)
5) Access to phone and internet
6) English-speaking
7) Have an assigned primary care provider at UPHS (excluding Lancaster General and Princeton)
8) Never received LCS at Penn Medicine

3.7. Participant Remuneration

All enrolled patients will be asked to complete a brief baseline survey and will receive $20 upon completion of the baseline survey. Additionally, all patients will be re-contacted approximately 4-8 weeks after enrollment to conduct a brief post-intervention survey. Patients with a scheduled telehealth visit (treatment arm) will be contacted within 1 week of completed appointment if the scheduled visit is longer than 8 weeks from enrollment. Patients who complete this post-intervention survey will receive an additional $10 upon post-trial survey completion.

Patients will receive payments through issuance of GreenPhire ClinCards that will be mailed to participants within 10 days of enrollment and completion of baseline survey. These ClinCards can be used in the same manner as a credit card. ClinCards can be re-loaded remotely with additional funds by study team members after completion of study activities.

4. Randomization

4.1. Groups
We plan to compare the effectiveness of two care arms, as follows:

Arm 1: Usual care
Patients in the usual care arm will be provided with contact information for the Penn LCS Program and encouraged to discuss LCS with their providers.

Arm 2: Intervention
Patients in the intervention arm will be invited to complete a telemedicine LCS counseling visit and asked for permission to be referred (name and phone number) to the LCS navigator at Penn Medicine to schedule the visit.

4.2. Assignment
Participants will be randomized individually to 1 of the 2 arms using REDCap randomization module (1:1 stratified by study batch). Patients will be randomized at the point of survey invitation due to the structure of REDCap randomization module and the study design.

5. Study Procedures

5.1. Eligibility Screening: Penn Chart Review
In order to assess potential eligibility, we will abstract the following variables from Penn Chart and/or Clarity:
- Name
- Address
- Email
- Birth date
- Prior lung cancer screening
- Smoking history (social history)
- Medical and family history (including cancer diagnoses and comorbidities)
- Phone number
- Medical record number

Patients who meet the following criteria will be invited to participate: a) aged 55-77; b) had a primary care or pulmonary visit at UPHS within the last 24 months (2019-2021); c) have never had a LDCT scan for lung cancer; d) are listed as current smoker within the medical record; e) English-speaking; f) have never been diagnosed with lung cancer; and g) have an assigned UPHS primary care provider listed in the medical record. All patients who meet eligibility screening criteria will be invited via email or mailed letter for study involvement. However, only patients who confirm additional eligibility for lung cancer screening based on US Preventive Services Task Force recommendations will be eligible for study enrollment assessed electronically prior to administration of baseline survey (Appendix B).

5.2. Recruitment
We will send electronic invitations and/or mail paper letters to all UPHS patients who meet the initial eligibility screening (Appendix A). Patients with an email listed in the medical record or with an active patient portal will be send the study invitation via email. Up to two reminder emails will be sent to patients who do not respond. Patients without an active email or active patient portal account will be mailed the invitation via letter. The invitation letter will indicate that study eligibility will be confirmed at the time of enrollment and provide brief details about the study.

To ensure our study is aligned with workflows of the Penn LCS Program, we will invite potentially eligible adults in randomly sampled, sequential batches (approximately four batches of 1,500 each for a total of 6,000 invited patients). Based on previous pragmatic trials (15), we anticipate that approximately 20% of these patients will respond to the invitation. Of these estimated 1,200 adults, we anticipate that 50% will meet lung cancer screening criteria and will enroll into the study, resulting in an estimated sample size of 600. After each batch, we will assess and adapt as needed to reach the sample size and to align with clinical capacity.

5.3. Waivers of Informed Consent and HIPAA Authorization

Consent Process:
Following confirmation of study eligibility within REDCap (Appendix B), participants will be given consent information prior to study commencement. Consent information will lay out the potential benefits and risk of participating in the study. Consent information will also clearly state that participation is completely voluntary.

Waiver of Written Consent:
This study involves no more than minimal risk to subjects. Lung cancer screening is recommended for eligible adults by the USPSTF, and LCS counseling is required for CMS reimbursement. Under the Affordable Care Act, LCS is provided without co-pay and is covered by insurance. Additionally, study questionnaires and materials present no more than minimal risk of harm and involve no procedure for which written consent is normally required. Consent information will be available to all participants for review prior to enrollment and their completion of study tasks indicates their ongoing consent (Appendix C). Patients will be instructed to document agreement to participate via REDCap before moving to the baseline survey but not required to sign their name.

Waiver of HIPAA authorization:
For purposes of recruitment and linkage of survey data to EMR data (primary outcomes), we are requesting a waiver of HIPAA authorization. This clinical trial meets the three criteria for a waiver of HIPAA authorization in accordance with the provisions for using protected health information (PHI) set forth in 45 CFR 46, § 164.512 (i) as follows: (1) the researchers require access to protected health information (PHI) in order to conduct the research, (2) The research cannot be practicably conducted without the waiver, and (3) the use or disclosure of PHI poses no more than minimal risk to participants. A request for Waiver of HIPAA form has been included in this protocol application.

5.4. Blinding

The primary analyst will be blinded to the randomization assignment. Drs. Rendle and Vachani (PIs) and the research coordinator will be unblended to facilitate referral to the LCS program. The research coordinator will record the randomization assignments on a master list and enter into REDCap using the randomization module. Assignments will be maintained by the research coordinator on a password protected computer in a locked office. The blind may be broken in the case of an emergency.

5.5. Allocation

Participants will be randomized in the REDCap platform to one of the two study arms, as described in §4.1. Patients are considered assigned to the Intention-to-Treat analyses upon confirmation of eligibility and enrollment in the study.

5.6. Baseline Survey
Following enrollment, all patients will be asked to complete a brief baseline survey (See Appendix D) accessible through REDCap, assessing demographics, lung cancer screening attitudes and beliefs, decisional conflict and satisfaction, smoking beliefs, and screening intention using measures previously applied in other studies (16-19).

5.7. Intervention Assignment
Following consent, patients will be randomized into one of the two treatment arms. Participants will subsequently receive follow-up information specific to their randomization arm. Participants in both arms will receive brief information within REDCap describing the benefits and harms of LCS using information from a validated decision tool developed by AHRQ (https://effectivehealthcare.ahrq.gov/decision-aids/lung-cancer-screening/patient.html). Patients in the usual care arm will then be provided with contact information for the Penn LCS Program, and encouraged to discuss LCS with their providers. Patients in the intervention arm will be invited to complete a telemedicine LCS counseling visit, and asked for permission to be referred directly to the LCS navigator in order to help schedule an appointment. They will also be given the option to directly contact the LCS navigator to schedule a telehealth appointment. For those patients in the treatment arm who agree to be referred, the research team will provide their name and phone number to the LCS navigator and s/he will contact the patients directly.

5.8. Telemedicine LCS Counseling Visits
Telemedicine counseling visits will be conducted using established clinical procedures for virtual or telephone visits at Penn Medicine and as recommended by the American College of Radiology for LCS. In accordance with reimbursement policies for lung cancer screening, these visits will be conducted by a physician or nurse practitioner within the Lung Cancer Screening Program at Penn Medicine. Counseling visits are covered without co-pay as standalone visits according to USPSTF guidelines and costs will not be covered by the study. LCS is an evidence-based practice and considered standard of care for those who are eligible and desire to be screened. Clinicians and patients retain full control regarding decisions to complete (or not) LCS counseling or LDCT.

5.9. Post-Intervention Surveys
All patients will be re-contacted approximately 6-8 weeks after enrollment to conduct a brief survey assessing quality of shared decision-making (if completed LCS counseling) (21), and LCS decision-making (16-19). Those who complete a telehealth visit will also be asked to evaluate their telehealth experience (20).

6. Data Management

6.1. Data Collection
All research data will be captured electronically via the EHR and REDCap. UPHS uses EPIC as its EHR platform. We will use REDCap for conducting the baseline and post-intervention surveys. We will extract clinical data directly from Epic including data on lung cancer screening counseling and uptake following enrollment, progress notes discussing LCS, and other data pertinent (e.g. patient and provider characteristics) to measuring primary outcomes.

6.2. Data Management
This study is staffed by a research support team that includes a data manager and statistical analyst who will have direct access to data submitted by patients. Additional study staff (project manager, research coordinator, investigators) will have access to patients' contact information

in order to coordinate study activities. Access to all study data will be limited to specifically designated researchers.

To link the survey data with the EHR data (to evaluate receipt of LDCT or LCS by primary care provider), we will send individualized links or access codes to each participants. REDCap is a secure survey and authorized to collect protected health information. For distribution of research incentives, patients will be asked to provide mailing address information.

6.3. Study and Data Monitoring

The co-Principal Investigators will monitor this study with the research team on a bi-weekly basis. They will review the study progress through regular electronic and in person communications.

6.4. Risks

The risks associated with this study are no more than minimal. There is the potential risk of breach of confidentiality. We will minimize this risk by using de-identified information whenever possible and by maintaining all identifiable information on a secure drive and/or in a HIPAA-compliant system (e.g. REDCap). Other risks include possible discomfort in disclosing information on screening knowledge, beliefs or practices. To minimize any discomfort with discussing this information, participants are free to skip any survey question.

6.5. Benefits

Participants may indirectly benefit from the study through improved awareness regarding lung cancer screening and by learning of their potential eligibility for lung cancer screening. For the health of society, the benefits of the study are substantial and include potential increase in the uptake of routine lung cancer screening, and increased knowledge of the cancer screening options and recommended screening intervals.

6.6. Risk-Benefit Ratio

Given the limited risk associated with participation in surveys, we anticipate that the benefits of this study will far outweigh the risks involved.

7. Analysis

7.1. Primary Endpoint

The primary endpoint is completion of LCS counseling, defined by completion of a telemedicine visit, in person counseling visit (CPT G0296), or documentation of LCS counseling in EHR provider notes. Secondary endpoints include completion of LDCT for LCS, reach (defined as proportion of patients who engage with the direct outcome divided by those who are invited to engage with the outreach), and referral or completion of tobacco cessation treatment.

7.2. Sample Size and Statistical Power Calculations

With a sample size of 600 patients across the two arms, the study be powered (1-β=80%, Two-sided α=0.05) to detect a minimum difference of 5.9- 11.4% in the primary outcome (LCS counseling) between the study arms, depending on completion rate (10-90%) of in controls.

7.3. Statistical Methods

Primary Analysis:

Intention-to-treat (ITT) analyses using logistic regression to assess the overall effect of the intervention on completion of LCS counseling among those who enroll.

Secondary Analysis:
Baseline survey and clinical data will be used to explore potential predictors (demographics, cognitive biases, and other factors) on screening intention and LDCT uptake. We will also explore potential differences by patient groups based on age, race, and sex. We will fit multivariable regression models with intervention, moderator, and interaction terms to assess effect modification based on significance of the interaction term. These analyses are exploratory.

8. Study Monitoring and Safety

8.1. Investigative Team
The study team is led by co-Principal Investigators, Drs. Katharine Rendle and Anil Vachani.

Dr. Rendle is an interdisciplinary behavioral scientist with expertise in healthcare delivery research, mixed-methods, observational data analysis and cancer prevention. Her work has focused primarily on cancer care delivery, cancer screening across organ types, shared decision-making, and patient-reported outcomes. As the co-PI, Dr. Rendle will be directly responsible for the design, execution, analysis, and reporting of all research activities and management.

Dr. Vachani is a pulmonary physician scientist with clinical and research interests in thoracic oncology and lung cancer screening. He is the Director of the Lung Nodule Program and is Co-Director of the Penn Lung Cancer Screening Program. As a Co-I and clinical partner, Dr. Vachani will oversee all aspects of the study and help to align study with clinical workflows and capacity.

All study investigators and staff at Penn have completed the online training program, Collaborative Institutional Training Initiative (CITI), and will maintain active certifications throughout the study. Penn team members are further required to maintain HIPAA certification and Good Clinical Practice certification. In aggregate, these materials provide systematic training in the fundamental issues underlying the responsible conduct of research.

8.2. Regulatory Approvals
The University of Pennsylvania IRB will serve as the IRB of record for this trial. The study has a dedicated project manager who will ensure that the most current version of the study protocol and supplementary materials are added into Penn's Human Subjects Electronic Research Application (HS-ERA) system. The project manager will additionally be responsible for submitting protocol-wide modifications and for reporting any deviations, exceptions, and reportable events within required timeframes to the co-PIs and IRB. A formal closure request will be submitted once study activity has been completed and there is no further access to identifiable subject data for research purposes.

8.3. Safety and Adverse Event Monitoring

Definitions

Adverse Event: An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal

- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

Relationship of AE to Study

The relationship of each adverse event to the study procedures will be characterized by the PIs and will be classified as either definitely related, probably related, unlikely to be related, or unrelated.

Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

The PI and study team will conform to the adverse event reporting timelines, formats and requirements of the IRB and DSMC. If a narrative report is submitted, the following information will be provided to all reviewing entities:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Any other events will be recorded and reported in accordance with institutional and federal policies.

Follow-up report
If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information will be submitted to the IRB and DSMC. The PI will be responsible for ensuring that all SAE are followed until either resolved or stable.

Investigator Reporting: Notifying the Penn IRB
The investigator will submit reports to the IRB within ten working days (with one exception) of events that meet the definition of an unanticipated problem involving risks to subjects or others. Exception: If the adverse event involved a death and indicates that participants or others are at increased risk of harm, the investigator will submit a report to the IRB within three days.

The investigator will submit reports to the IRB and DSMC in accordance to their current reporting requirements:

- All Grade 3 or higher events (AE or SAE) within 10 business days of knowledge.
- All unexpected deaths within 48 hours of knowledge.
- All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Stopping Rules: n/a

Data and Safety Monitoring Plan
Safety will be monitored on an ongoing basis by the PIs and the study team. The PI or designee will review the study charts to evaluate events at each subject interaction to ensure the grade, relationship to the study procedure, expectedness and the course of action for each subject is documented. The PI or Sub-investigator is ultimately responsible for assigning grade and attribution.

9. References

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10. Appendices