Empowering patients' Lung Cancer Screening uptake (Empower LCS)

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1. PROTOCOL SYNOPSIS

Study Number	UCI 23-107
Study Title	Empowering patients' Lung Cancer Screening uptake (Empower LCS)
Development Phase	II
Funding Source(s)	Anti-Cancer Challenge Pilot Award
Operational Changes during the COVID-19 Pandemic	N/A
Sources of Study Drugs	N/A
Number and Identity of Study Sites	University of California Irvine Health
Study Rationale	Utilization of lung cancer screening (LCS) using Low Dose CT (LDCT) among those eligible is low. We are assessing feasibility of a multi-level intervention to improve lung cancer screening uptake.
Study Design	Single arm longitudinal study
Study Objectives	1. Assess feasibility of our multi-level intervention in increasing patients' LCS knowledge, having a LDCT ordered, and patients' receipt of LCS with LDCT. 2. Assess LCS-eligible patients' and their providers' perceptions and barriers towards LCS. 3. Describe patients' & providers' experience with the intervention using a mixed-methods approach.
Planned and Maximum Sample Size	70 patient participants (English, Spanish, and Vietnamese speaking), and between 20-40 non-patient participants.
Duration of Study Participation	Patient participants: 6 months. Up to 15 patients will be asked to participate in a 30-min interview after 6 months completion of the study. Non-patient participants: One time. 5 non-patient participants will be asked to participate in a 30-min interview within 3 months of last patient enrollment.
Indication(s) Under Study	Patients eligible for lung cancer screening
Inclusion Criteria	1. Aged 50- 80 years of age.

	2. Be able to Speak English, Spanish, or Vietnamese 3. Must have a primary care provider 4. Meeting the LCS eligibility criteria based on self-reported smoking history (for UCI and non-UCI Health patients) as well as documented in EMR (for UCI Health patients) and confirmed prior to enrollment
Exclusion Criteria	1. No prior history of lung cancer 2. No chest CT for any reason in the last 12 months based on self-report (for UCI and non-UCI Health patients) and UCI EMR (for UCI Health patients) 3. No history of Alzheimer's disease or dementia
Study Intervention	Our proposed intervention, informed by the Health Belief Model[19], is a multi-level intervention including: (1) PCP notifications of patients' LCS eligibility (addressing provider time constraints and barrier in identifying eligible patients); (2) patients' education (addressing knowledge barriers); (3) patients' referral to financial navigation resources (addressing health-related social risks); and (4) patients' reminder to discuss LCS during PCP visit.
Baseline Assessments	Baseline survey at enrollment
Efficacy Assessments	Follow-up survey 6 months after enrollment
Statistical Methodology	Descriptive measures, comparison of pre- and post- intervention endpoints
Efficacy Endpoints	Primary end point is order of LDCT within 6 months after enrollment assessed with self-reported surveys (for UCI and non-UCI Health patients) and EMR data extraction (for UCI Health patients)

Figure 1 Study Schematic

A. Pre-Screening (identify potentially eligible population)
UCI Health IT Enterprise will be queried for a list of patients 50-80yrs of age and speak English, Spanish, and Vietnamese. If they have a history of smoking or an unknow history of smoking and have a Primary Care Provider. Primary care clinics list of patients and EMR will also be manually checked for potential eligible patients. We will also distribute study flyers to community clinics and Vietnamese and Spanish speaking social media, and news outlets.

B. Screen/Approach Patients:
Approaching all potentially eligible patients via Redcap survey, phone, mail or in person in the clinic:
- Verify study eligibility by a short 2-minute survey.
- Recruit eligible subjects for participation.

C. Consent Patients:
Obtain written informed consent (DocuSign or paper).

D. Baseline Procedures
Encourage participants to complete baseline survey.

E. Deliver Interventions
(1) PCP notifications of patients' LCS eligibility; (2) patients' education; (3) patients' referral to financial navigation resources; and (4) patients' reminder to discuss LCS during PCP visit.

F. Follow up Procedures:
Participants complete a follow-up survey 6 months post-enrollment.
Non-patient participants (Primary Care Providers) will complete a survey

G. Qualitative Interview
15 patients will be randomly selected to undergo a 30-minute interview.
5 providers with highest number of enrolled patients in the study will undergo a 30-minute interview

Table 1 Schedule of Events

	Pre-Screen	Screen	Baseline	Primary Care Appointment	6 months Follow-up	Provider Survey	Interview
UCI Health IT inquiry	X						
Distribution of flyer to community clinics and Spanish and Vietnamese speaking social media and news outlet	X						
Screening 2-min survey		X					
Informed Consent			Prior to PCP appointment				
Baseline Survey			After informed consent prior to PCP appointment				
Intervention delivery				After baseline survey, prior to PCP appointment			
Follow-up survey					Within -14 and +30 days of 6 months follow-up		
Provider Survey						Within 3 months of last patient enrollment	
Interview							Within 30 days of patient or provider completion of their survey.

2. ABBREVIATIONS AND ACRONYMS

Abbreviation	Definition
AE	Adverse Event
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
EMR	Electronic Medical Record
HRPP	Human Research Protections Program
LCS	Lung Cancer Screening
LDCT	Low Dose CT
NCI	National Cancer Institute
SAE	Serious Adverse Event
USPSTF	United States Preventive Services Task Force

3. BACKGROUND AND RATIONALE

Lung cancer is the leading cause of cancer-related mortality, with 1.8 million annual deaths worldwide.[1] Lung cancer screening (LCS) with low-dose computed tomography (LDCT) is shown to decrease mortality rate of lung cancer by 20%, compared with chest x-ray alone.[2] From 2015, both private and public health insurance began to cover lcs with ldct.[3] However, lcs uptake remains low,[4] with only 12.8% of LCS-eligible patients receiving ldct in 2019,[5] and 55% of those with a baseline LDCT returning for ldc in the subsequent 12-36 months.[6] Further, white race is twice more likely to be adherent to lcs compared to races other than white.[6] The 2021 US Preventive Service Task Force (USPSTF) update expanded the eligibility criteria and recommended high-risk populations (aged 50–80 years old, have a 20 pack-year smoking history, and currently smoke or have quit within the past 15 years) to receive annual LDCT to screen for lung cancer.[7]

There are several barriers to LCS. **Provider barriers** includes the failure of the electronic medical record (EMR) to notify providers of eligible patients (most common), patient refusal, perceived high false-positive rate leading to unnecessary procedures, provider time constraints, and patients' lack of insurance coverage.[8] Identifying eligible patients through EMR is often challenging as smoking pack-year data is either not complete or discordant (92.6% in one study) with patients' self-reported data obtained during patient-provider shared decision making conversations regarding LCS.[9] This results in lack of trust of the primary care providers (PCP) to use EMR data for such purposes.[10] **Patients' barriers** to LCS includes concerns regarding insurance coverage and co-pay for both screening and treatment (if diagnosed with cancer), access to convenient care, fear of a positive screening result or radiation exposure, and lack of understanding that lung cancer correlates with smoking history.[11,12] Prior research assessing perceptions and barriers towards LCS and interventions to address barriers among diverse non-white and non-English-speaking population is limited. Interventions addressing LCS knowledge barriers have shown an increase in patients' knowledge or decisional certainty,[13,14] but were not sufficient to increase receipt of LCS.[13-16] On the other hand, interventions involving direct patient outreach (e.g., reminders to call and schedule LCS) or patient navigators addressing multiple barriers were more successful in increasing LCS uptake.[17,18]

Our proposed intervention, informed by the Health Belief Model[19], is a multi-level intervention including: (1) PCP notifications of patients' LCS eligibility (addressing provider time constraints and barrier in identifying eligible patients); (2) patients' education (addressing knowledge barriers); (3) patients' referral to financial navigation resources (addressing health-related social risks); and (4) patients' reminder to discuss LCS during PCP visit. We propose to assess perceptions and barriers towards LCS and test our intervention among 0 English-, Spanish- and Vietnamese-speaking LCS-eligible patients with a scheduled PCP visit at any of UCI primary care clinics including FQHC or at non-UCI Health clinics in the next five months.

4. STUDY OBJECTIVES

4.1. Primary Objective

4. Assess feasibility of our multi-level intervention in increasing patients' LCS knowledge, having a LDCT ordered, and patients' receipt of LCS with LDCT.

4.2. Secondary Objectives

1. Assess LCS-eligible patients' and their providers' perceptions and barriers towards LCS.
2. Describe patients' & providers' experience with the intervention using a mixed-methods approach.

5. INVESTIGATIONAL PLAN

5.1. Indications Under Study

Patients eligible for lung cancer screening

5.2. Overall Study Design

We will conduct a single arm longitudinal clinical trial of 70 LCS-eligible patients with a PCP appointment at UCI health within five **months** after enrollment. All patients will complete a baseline survey to assess their perceptions and barriers towards LCS and will receive a multi-level intervention. All patients will complete a survey at 6 months post-enrollment to assess changes in perceptions and knowledge, receipt of an order for LDCT or completion of LDCT, and experience with intervention. All primary care providers of enrolled patients will be sent a survey 3 months after last patient enrollment to assess providers' barriers to order LCS. We will interview randomly selected up to 15 patients and 5 PCP participants with highest enrolled patients in the study, who consent to be interviewed to assess experience with the intervention.

5.3. Study Segments and Visits

The different phases of the study are illustrated in Figure 1, with details of assessments schedule in the main study segments given in Table 1.

5.4. Number of Subjects

70 patient participants, and between 20-40 non-patient participants.

5.5. Definition of Completers

Participants who complete all study procedures are considered completers. For patients this include consenting, completing baseline survey, receiving study intervention and completing the 6 months follow-up survey.

5.6. Study Stopping Rules

Not applicable.

6. STUDY POPULATION

6.1. Inclusion Criteria

Patients with the following characteristics are eligible for enrollment into the study:

Aged 50- 80 years of age.

Be able to Speak English, Spanish, or Vietnamese

Must have a Primary Care Providers.

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Meeting the LCS eligibility criteria based on self-reported smoking history as well as documented in EMR and confirmed prior to enrollment (current or former smoker with 20 pack year smoking history)

6.2. Exclusion Criteria

The following patients will not be eligible for participation in the study:

No prior history of lung cancer

No chest CT for any reason in the last 12 months based on self-report (for UCI-Health and non-UCI Health patients) and UCI EMR (for UCI-Health patients)

No history of Alzheimer's disease or dementia

7. STUDY PROCEDURES

7.1. Pre-Screening

UCI Health Patients:

UCI clinical data warehouse will be inquired every week for a list of patients and their contact information, who are 50-80 years old, speaking English, Spanish or Vietnamese, and have a primary care provider, who are current or former smokers or have an unknown smoking history in EMR, and have no history of lung cancer, Alzheimer's disease or dementia, and have not received a chest CT or LDCT in the last 12 months. We will further inquire from primary care providers about their potentially eligible patients. EMR will also manually be reviewed to assess eligibility and generate an additional list for recruitment. We will take a note of patients with primary care appointment in next 5 months so that we have in person outreach.

We will send an email outreach with the study information, an option to opt out if not interested, and a short 2-min REDCap survey to verify LCS eligibility if interested in participating. For non-English speaking patients, the email outreach and survey will be sent in their preferred language. The survey includes questions on smoking history, prior history of lung cancer, and prior receipt of chest CT in the last 12 months.

To ensure our sample size is representative of population, we plan to have phone outreach, text message outreach, in person clinic visits to directly recruit participants, or mailing surveys (by bilingual research team) to patients who do not have an email address or do not respond to the email outreach, a common condition among non-English speaking patients.

Non-UCI Health patients

Additionally, we will conduct outreach to patients outside of the UCI Health system.

Outreach materials, such as flyers with QR codes, will be distributed to local clinics serving Latino and Vietnamese populations to be placed in their waiting rooms. We will also distribute these flyers via social media groups aimed at Spanish- and Vietnamese-speaking population. Lastly, working with cancer center community outreach program we distribute the flyers during community events. We may advertise the flyers with 1-2 message during local radio or TV outlets.

Patients who are interested will scan the QR code to easily connect with our team. They can also call us or email us if interested. We will also provide drop-off boxes in the clinics for interested patients to leave their contact information.

The 2-minute pre-screening survey for non-UCI Health patients will include inquiring about the name and contact information for their primary care doctor.

Non-UCI Health providers will not be engaged with human subject research at any point.

7.2. Non-eligible patients

Patients who do not meet the eligibility criteria based on the survey will be asked to complete a HIPAA authorization form sent to them via DocuSign, fax or mail, based on patients' preference.

Given documenting smoking history in EMR during health encounters is being implemented at UCI, we plan to compare EMR smoking history data with patients' self-report to assess for accuracy. This only applies to UCI Health patients.

7.3. Informed Consent

Patients who complete the LCS eligibility survey and meet the study eligibility criteria will be then contacted via phone by a study coordinator speaking the patients' language for a study overview and consenting. A signed and dated written informed consent form (ICF) will be obtained from the patient via DocuSign, fax or mail. A signed copy of each ICF will be given to the patient or they can download it via REDCap.

7.4. Screening Confirmation

Patient information should be entered into OnCore within 5 business day of consent. Each site is responsible for assigning subject ID.

7.5. Baseline Survey

Patients will be asked to complete a 15-min survey either on the phone or online via REDCap based on preference. This survey includes validated measures utilizing the Health Belief Model[20,21] to assess perceived risk of getting lung cancer, benefits and barriers to LCS, and self-efficacy for LCS, prior receipt of any screening exam, overall willingness to undergo LCS with LDCT, and engage in receiving LCS educational information. We will further screen for health-related social risks such as financial hardship, difficulties in paying for food, transportation, and housing instability as a barrier to receipt of LCS, and query on demographics, insurance, health literacy, zip code (to assess neighborhood socioeconomic status), and presence of other comorbidities and healthy behaviors. Participants with completed survey will be sent a $15 gift card. Survey materials will be available in English, Spanish, and Vietnamese.

7.6. Study Intervention

Consented patients completing baseline survey will receive usual care which includes a provider flag in EMR on their eligibility for LCS if their smoking history is complete.

Our intervention includes:

(1) Primary Care Provider notification of patients' LCS eligibility, and their self-reported barriers to receipt of LCS based on baseline survey. The notification will be sent using an EPIC secure message and via email within 2 weeks prior to scheduled PCP visit. If a patient cancels or reschedules the appointment, the message will still be sent within 2 weeks of the initial appointment. Prior to study activation, all UCI PCPs will be emailed and notified of our study.

For non-UCI Health PCPs, reminders to discuss LCS will be sent via secure email or direct phone calls to their office. Non-UCI Health PCPs will not directly engage in research activities and will instead continue to admisnter standard patient care. Non-UCI Health PCPs will not represent the study.

(2) patient education of LCS: patients will be mailed (paper) and emailed (PDF from; if have an email address) information (in preferred language) on lung cancer risk, LCS benefits, harms, false positive rates, recommendations of follow-up for positive results, and exam insurance coverage. Publicly available resource "Should I Screen"[22] and baseline survey data will be used to create material.
(3) patients' referral to financial navigation resources: Patients who self-report needing help with health-related social risks at baseline will be mailed (paper) and emailed (PDF

from; if have an email address) a brochure (in preferred language) from patient advocate foundation (PAF), a national non-profit financial navigation organization, where patients can self-refer;

(4) patients' reminder to discuss LCS during PCP visit: within 2 weeks prior to appointment, all patients, regardless of their site for care, will receive a text message or a phone call (if not having a phone that receives text messaging) encouraging patients to discuss the LCS with their provider.

7.7. Patient Follow-up

Patients will be surveyed 6 months after enrollment to assess self-reported LCS discussion with PCP, provider order of LDCT, and patients' receipt of LDCT. We will also extract these from EMR only for UC-Health patients. Patients will be queried on LCS perceived risks, benefits, barriers, and self-efficacy, experience with intervention including educational material, reminders, and self-referral to PAF if PAF brochure was received.

Surveys will be completed online (REDCap), on the phone or paper (mailed with a pre-stamped pre-addressed envelope) based on patient's preference. Patients with completed survey will receive a $15 gift card.

7.8. Non-patient participant Follow-up

Any of the UCI Primary Care providers who receive a provider notification of their patients' LCS eligibility as part of the study will be eligible to participate. Three months after last patient enrollment, we will send an electronic REDCap information sheet to all eligible providers and ask them to complete an online 10-minute survey.

The survey includes questions pertaining to provider demographics, clinical practice, perception regarding barriers to LCS, awareness of CMS beneficiary eligibility criteria for LDCT using a validated questionnaire,[8] providers' experience with EMR flags they receive for patients' LCS eligibility as part of usual care, as well as their experience with the patient-specific LCS eligibility notification they received as part of the study and whether that prompted them having a LCS discussion with their patients. Additionally, we will inquire about their interest in future development of a provider-directed educational material. Survey participants will receive a $15 gift card. We expect 20-40 providers participate in the survey.

7.9. Qualitative interviews with patient and non-patient participants

We will conduct in-depth phone interviews with randomly selected 15 patients and 5 PCP participants with highest number of enrolled patients in the study. The Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework will be used to guide the evaluation questions and examine the effectiveness of the intervention and implementation outcomes.[101]

We will ask patients and providers to describe any barriers to LCS completion (for patients) and ordering (for providers) and describe their experience with use of various components of the intervention, as well as feedback on what they liked and disliked about the intervention, and what they would change to make it more helpful or engaging. Participants will be recruited via phone by the study coordinator, and interviews will be conducted on the phone, video conference or in person. We expect that patient interviews take 30 minutes, and provider interviews take 20 minutes. Interview participants will receive a $40 gift card.

8. EFFICACY ASSESSMENTS

Primary end point is order of LDCT within 6 months after enrollment assessed with self-reported surveys (for UCI-Health and non-UCI health patients) and EMR data extraction (for non-UCI Health patients). Remainder of outcomes is show in Table 2.

Table 2 . Study Outcomes, Measures and co-variates		
Efficacy Outcomes		
LDCT order for LCS	6 mo	Survey and EMR
Receipt of LDCT for LCS	6 mo	Survey &EMR
Pt and PCP LCS discussion	6 mo	
Pt perceived risks, benefit, barriers, and self-efficacy using LCS health belief model[21]	Baseline & 6 mo	Survey
Process Evaluation Outcomes		
Rate of concordance of EMR and self-report smoking hx	Baseline	Survey& EMR
Showing up to PCP visit	6 mo	
Self-referral to PAF	6 mo	Survey
Pt and provider experience with intervention components	6 mo	Survey& interview
Provider perceived barriers and knowledge of LCS	Beginning 9 mo after first pt enrollment	Survey
Covariates		
Sociodemographics, insurance, neighborhood deprivation index, health literacy, comorbidities	Baseline	Survey
Financial worry[23,24] and health-related social risks[25]	Baseline & 6mo	Survey

- Any mention of ER is only for UCI Health patients.

9. SAFETY AND TREATMENT-EMERGENT ADVERSE EVENT REPORTING

We do not anticipate any adverse events related to participation in this study beyond usual care.

If a participant report feeling distressed as a result of study participation, they may choose not to continue or to complete them and/or speak with the research team.

9.1. Reporting Protocol Violations and Protocol Deviations

Protocol Violation are defined as an accidental or unintentional change to or noncompliance with the IRB-approved protocol that increases risk or decreases benefit

and/or affects the subject's rights, safety, welfare, and/or the integrity of the data. Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent. [Reference: Policy #57 UCI HRPP Policy and Procedure Glossary].

Protocol Deviations are defined as an accidental or unintentional change to the research protocol that does not increase risk or decrease benefit or have a significant effect on the participant's rights, safety or welfare, or on the integrity of the data. Deviations may result from the action of the participant, researcher, or staff. Examples: a rescheduled study visit, or failure to collect an ancillary self-report questionnaire data (e.g., quality of life) see Policy #57 UCI HRPP Policy and Procedure Glossary (https://www.research.uci.edu/compliance/human-research-protections/hrp-policy-library/hrppPolicies.htm).

9.2. Standard Reporting Requirements for Adverse Events

Adverse events, serious adverse events, deviations, violations, and unanticipated problems must be entered into the clinical trial management system, OnCore and/or Advarra EDC and must also be reported to the following entities according to the timelines mentioned in the chart below. Serious adverse events collection will start at the time patient signs consent until 30 days after the end of intervention. Adverse events will be collected from the time the research patient begins treatment until 30 days after the end of intervention. All adverse events/serious adverse events should be followed until resolution or stabilization, or the subject dies or withdraws consent from participation in the study. Table 3 lists the various reporting schedules for AEs by event type.

Table 3 Standard Reporting Requirements for Adverse Events by Event Type

Event Type	Coordinating Center/Principal Investigator	UCI IRB	CFCCC DSMB
Unanticipated Problem	Within 24 hours from date the site is aware of the event, the site should enter this information into OnCore and/or Advarra EDC.	Within 5 business days submit a report within KR Protocols.	Within 5 days from date PI is aware of the event. This information must be reported into OnCore and/or Advarra EDC.
AEs and SAEs (non-Unanticipated Problem)	Please refer to section 7.5 for reporting timeframes on AEs and SAEs.	N/A	Please refer to section 7.5 for clarification

Event Type	Coordinating Center/Principal Investigator	UCI IRB	CFCCC DSMB
			on reporting timeframes for AEs and SAEs.
Noncompliance	N/A	N/A	Please refer to section 7.5 for reportable deviations or violations.
Serious or continuing noncompliance	Within 24 hours via email	Within 5 business days submit a report in Kuali Protocols.	Within 5 days from date PI is aware of the event.
Prospective/Planned Deviations	At least 5 business days prior to the event via email	At least 48 hours prior to date the request is needed by. Submit a Prospective Deviation Request within Kuali Protocols.	At the time of progress review as aggregate reports

Adverse Event/Serious Adverse Events

Event Type	Reporting Timeframe
Serious Adverse Events (all attributions) that meet all of the following criteria: ▪ Unexpected ▪ Grades 3-5 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
Adverse Events that meet all of the following criteria: ▪ Unexpected ▪ Study related (possibly, probably, or definitely) ▪ Grades 3-4 ▪ Occurring during treatment or within 30 days of the end of treatment*	5 business days from date the PI is aware of the event
All other Adverse Events and Serious Adverse Events should be reported as noted in the 'Recording of Events' section	Prior to each scheduled progress review

** Investigators are not obligated to actively seek information regarding the occurrence of new AEs or SAEs beginning after the 30-day post-treatment period. However, if the investigator learns of such an event and that event is deemed relevant to the study, he/she should promptly document and report the event.*

Deviations/Violations

Event Type	Reporting Timeframe
Violations as defined above (e.g. wrong dosage of drug administered, safety procedures not being conducted at specific time points)	5 business days from the date the PI is aware of the event
Deviations as defined above, including: ▪ Planned deviations (e.g. rescheduling a visit that will be out of window due to a holiday) ▪ Unplanned deviations (e.g. rescheduled visit, a missed routine safety laboratory test for a participant with previously normal values)	Prior to each scheduled progress review

10. STATISTICAL METHODS

10.1. Planned and Maximum Sample Size

A sample size of 70 patients is feasible given the limits of the study timeline and budget and will allow us to characterize key patient variables.

10.2. Data Analysis Plan

This is a minimal risk/Exempt study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP), as shown in Table 4.

Table 4 Risk Levels as Defined in the Chao Family Comprehensive Cancer Center Data and Safety Monitoring Plan

Risk Level	Definition	DSMB Monitoring
Level 1	**High Risk** - There is the prospect of direct benefit to the subject, trial risks are high, or there is significant uncertainty about the nature or likelihood of adverse events. Example: • Trials where the Principal Investigator holds the Investigational New Drug (IND) / Investigational Device Exemption (IDE). • Gene therapy, dendritic cell products from GMP suite, phase I/II development and phase I studies, first in human, etc.	Every two months after subject enrollment

Level 2	**Medium Risk** - Trials where risks are recognized as being greater than low risk, but are not considered high. There is a medium to high probability of a moderate-severity event occurring as a result of trial participation. Example: • FDA exempt IND/IDE trials of any phase.	Every six months after subject enrollment
Level 3	**Low Risk –** Trials that are greater than minimal risk (45 CFR 46.102 (j)). There is a moderate probability (25-50%) of the occurrence of a low-severity event (grade 1 and 2) that is completely reversible or the likelihood of serious harm occurring is low. Example: • Trials that may include interventions or invasive procedures that present low risks, reasonably commensurate with those expected in medical or dental practice, but do not fit in an IRB-expedited review category • Post-marketing studies (e.g. Phase IV drug/device study (as defined by FDA) previously determined to be low risk).	Every twelve months after subject enrollment
Level 4	**Exempt** – Trials that are industry-sponsored, NCTN-sponsored, and/or trials monitored by an external DSMB. Also includes trials that are IRB-exempt and IRB-expedited protocols (determined by the IRB as minimal risk). *Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. (45 CFR 46.102 (j))* Example: • Trials that qualify under IRB expedited categories 2-7 and category 13. • Trials that are IRB-exempt, and non-interventional/non-therapeutic trials.	N/A

10.3. Safety and Tolerability Analyses

Not applicable

10.4. Statistical Analyses

We will work with the Biostatistical Shared Resource, and report proportion of LDCT order, receipt of LDCT, and LCS discussion using descriptive measures. We will compare pre-post measures of perceived risk to lung cancer, LCS benefits, barriers, and self-efficacy using paired t-tests or Chi-squared tests, where appropriate. Multivariable regression analyses will be performed adjusting for covariates. We will report rate concordance of EMR and self-reported smoking history. Qualitative interviews will be translated and transcribed verbatim, and they will be reviewed and discussed iteratively using a "theoretically-driven thematic analysis" approach.[26] The coding sequence will be conducted on a line-by-line unit of analysis using the Dedoose online system.[27] We will use deductive and inductive approaches,[103,104] organizing the data according to the domains in the interview guide and then open code the transcripts and inductively search for specific patterns and themes in each domain. We will develop the codebook based on the domains, emergent themes, and discussion.[105] Coders will independently (and then collectively) examine and assemble coded data to identify themes within categories and relationships among them.

11. STUDY MANAGEMENT

11.1. Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by their own institution's Conflict of Interest (COI) Committee, with documentation of this process maintained in the study file.

11.2. Institutional Review Board (IRB) Approval and Informed Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

The Institutional Review Board (IRB) must review the protocol and the related Informed Consent Form (ICF) prior to study initiation and provide signed and dated documentation of their approval. The IRB must also approve any protocol or ICF amendments prior to their implementation, again providing signed and dated proof of approval.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA

Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3. Patient Registration Procedures

Prior to registration, eligibility criteria must be confirmed by the PI and study team. The following items must be reviewed and completed prior to beginning performing any Screening Assessments in Cycle 1:

1. Source documentation required to confirm eligibility which includes patient self-reported screening survey and data from UCI Health IT Enterprise.
2. Signed Informed Consent Forms

11.4. Data Completion

All investigator-initiated treatment trials require that adverse events, serious adverse events, deviations, and unanticipated problems be entered into the OnCore clinical trial management system and/or Advarra EDC. All entries must be entered in OnCore and/or Advarra EDC within the specified time intervals from the date the Investigator becomes aware of the adverse event, serious adverse event, violation, deviation, or unanticipated problem. Adverse events and violations/deviations and adverse events that are unanticipated problems that require prompt reporting to the DSMB must be entered into OnCore and/or Advarra EDC according to the timelines as specified.

Data collected in this study will be entered into Advarra EDC. The Investigator is responsible for ensuring all entries are accurate and correct. The Investigator must maintain accurate source data that support Advarra and OnCore data entry. Details of data entry procedures for OnCore can be found in the Study Manual.

11.5. Data Management and Monitoring/Auditing

11.5.1. Quality Assurance

The CFCCC Stern Center for Cancer Clinical Trials and Research Quality Assurance Unit will conduct monitoring and auditing activities as per the UC Irvine CFCCC Quality Assurance Monitoring and Auditing Plan and at the discretion of the CFCCC DSMB in order to ensure patient safety and data integrity oversight. By conducting internal monitoring and auditing, the CFCCC will ensure compliance with high quality standards and all applicable regulations, guidelines, and institutional policies. Trial monitoring and auditing may be completed remotely or on-site by the Quality Assurance Officer.

11.5.2. Data and Safety Monitoring Plan

This is a minimal risk/Expemt study, as defined in the Chao Family Comprehensive Cancer Center (CFCCC) Data and Safety Monitoring Plan (DSMP) because it is a non-therapeutic trial.

The Principal Investigator (PI), co-investigator, clinical research coordinator, and statistician are responsible for monitoring of data and safety for this study. For studies that have stopping rules for safety and efficacy, the PI will be responsible for the implementation and make changes as applicable. The CFCCC Data and Safety Monitoring Board (DSMB) is an independent body responsible for the safety of study subjects as well as the data integrity of the protocol. Data and safety will be reported to the DSMB with submission of progress reports that include aggregated reports of adverse events, serious adverse events, deviations, and violations. In addition, certain adverse events, serious adverse events, deviations, violations, and unanticipated problems will be reported promptly to the DSMB for review according to Section 9.2 and Section **Error! Reference source not found.**.

11.6. Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Due to restrictions instituted during the COVID-19 pandemic, planned clinic visits may be performed via telemedicine at the discretion of the Principal Investigator, following the guidelines established in the CFCCC Standard Operating procedure "Interim Standard Operating Procedure: Clinical Trial Enrollment and Operations during the COVID-19 Pandemic" (URL: \\hs.uci.edu\myshare\Cancer Center Research\COVID-19\Research\SOPs and Guidelines). Whenever possible, on-site clinic visits will be replaced by telemedicine visits between the clinic staff and on-study patients.

Emergency Modifications may be enacted if needed to ensure the safety, and well-being of the study patients. Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

All other planned deviations or violations from the protocol must have prior approval by the Principal Investigator and the IRB. Please refer to Section 9.1 for more information on how protocol deviations and violations are defined. It will also provide instructions on when and who to contact and obtain approval from for prospective deviations. Protocol deviations should also be reported to UCI IRB, UCI CFCCC Stern Center policies and the participating site's IRB policies.

11.7. Protocol Amendments

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an

amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required. Both the amended protocol and the amended ICF must be reviewed and approved by the IRB prior to being implemented.

11.8. Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least 2 years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until 10 years after the completion and final study report of this investigational study.

11.9. Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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