PROTOCOL AMENDMENT #3

LCCC 1945: Improving Quality of Life after Thoracic Surgery using Patient Reported Outcomes

AMENDMENT INCORPORATES (check all that apply):
_x_ Editorial, administrative changes
___ Scientific changes
___ Therapy changes
___ Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:
The purpose of this modification is to change the planned closeout for the study due to low survey completion rates and negative preliminary findings related to long-term QOL outcomes. Affected participants will be notified of this change by email. We plan to discontinue 2-year follow-up for those currently active in the study.

List of updates to the protocol:
Section 4.1 Updated to reflect that some patients will have a shortened participation period due to early discontinuation of study procedures.
Section 4.2 Updated to reflect that some patients will have a shortened participation period due to early discontinuation of study procedures.

THE ATTACHED VERSION DATED October 05, 2023 INCORPORATES THE ABOVE REVISIONS
ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1945: IMPROVING QUALITY OF LIFE AFTER THORACIC SURGERY USING PATIENT REPORTED OUTCOMES:

Principal Investigator

Gita Mody, MD, MPH
3040 Burnett-Womack Building
Campus Box 7065
Chapel Hill, NC 27599-7065
Phone: (984) 966-3382
Fax: (919) 966-3475
Email:gita_mody@med.unc.edu

Co-Investigator(s)
Ethan Basch, MD, MSc
Antonia Bennett, PhD
Benjamin E. Haithcock, MD
Jason M. Long, MD, MPH
Lauren Hill, DNP

Biostatistician
Allison Deal
Mian Wang

Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: Thoracic Surgery Foundation (completed), American College of Surgeons and Lineberger Comprehensive Cancer Center

Version Date: 10/05/2023

LCCC 1945: IMPROVING QUALITY OF LIFE AFTER THORACIC SURGERY USING PATIENT REPORTED OUTCOMES:

Principal Investigator
Gita Mody, MD, MPH
3040 Burnett-Womack Building
Campus Box 7065
Chapel Hill, NC 27599-7065
Phone: (984) 966-3382
Fax: (919) 966-3475
Email: gita_mody@ med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Gita Mody, MD

PI Signature: _____

Date:_____

Version Date: 10/05/2023

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

In this feasibility study, up to 140 patients undergoing elective thoracic surgery will be randomized to one of two arms to complete PRO (patient reported outcome) symptom monitoring. The two arms are 1) active symptom monitoring and 2) passive symptom monitoring. The participants randomized to active symptom monitoring will have alerts sent to their clinicians when their PRO symptom scores exceed baseline discharge day scores (when discharge day scores are available) by 2 points or more, or when 'severe' or 'very severe' symptoms are reported. Participants randomized to the passive PRO monitoring arm will complete the same PROs as participants in the active monitoring arm, but will not have alerts sent to their clinician.

The overall goal of this study is to assess whether collecting and monitoring patient-reported data is feasible as part of clinical care of thoracic surgery patients, and whether these data are useful for clinicians and patients. Among these 140 patients, a subset of approximately 40 patients and their 40 caregivers will be chosen to complete a semi-structured interview, if willing, to assess patient experience with monitoring experience.

1.2 Background

Patient-centered outcomes after surgery go beyond traditionally measured morbidity and mortality to include QOL [11]. Patients undergoing thoracic surgery strongly value communication from their providers about anticipated physical functioning post-operatively [12, 13]. Patients who require thoracic surgery are older, have comorbidities, and have greater decreases in QOL after often morbid treatments compared to other patients [14]. Therefore, 90-day readmissions after thoracic surgery remain high at 18%, largely due to symptomatic adverse events including post-operative complications and new cardiopulmonary diagnoses [4, 15]. While symptom severity and physical functioning worsen for up to 6 months after thoracic surgery [16-18], pain and QOL do return to baseline by 12 months [19], suggesting a window in the first year after surgery during which PROs can be better monitored and managed.

In non-surgical populations, management of patient-reported symptoms has been extensively linked to improvements in care delivery including readmissions. The NIH has developed a PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which is a validated library assessing the presence, frequency, severity, and interference with usual activities of symptoms. Responses are provided by patients on a 5-point Likert scale with recall being over the prior week [20]. PRO-CTCAE is feasible for use in a variety of patient populations [21]. In surgical patients, PROs have been used as clinical outcomes, for quality improvement, and as outcomes in comparative effectiveness research [22]. In thoracic surgery patients specifically, PRO assessment through weekly

telephone surveys has demonstrated symptom improvement; however, items assessed were standard cancer-related and one surgical specific symptom. Further, only 60% of symptom alerts lead to intervention by clinicians [8].

Currently, PROs including symptoms and QOL are not routinely collected in thoracic surgery patients. Challenges include selecting a comprehensive, sensitive instrument, time and knowledge required to administer and analyze responses, and integration into existing systems for outcomes measurement [9]. Nonetheless, a pilot study integrated empirically selected symptom items from PROMIS with the Society of Thoracic Surgeons (STS) National Database [16]. The potential value of using PROs in perioperative care is multifaceted and includes shared-decision making, increasing patient satisfaction, and prediction and improvement of overall outcomes [9]. Further research on effective implementation of thoracic surgery specific PRO instruments is required.

1.3 Purpose and Rationale

Patients undergoing thoracic surgery report maintaining independent physical functioning and quality of life (QOL) are important and influence their treatment decisions [1]. Research has shown readmissions, physical debility, and declines in QOL are common after thoracic surgery but has not identified solutions to improving these problems [2-4]. The rationale of this research is improvement of the patient experience and reduction of readmissions through management of symptoms after thoracic surgery.

A potential approach to managing symptoms after thoracic surgery is using patient-reported outcomes. Assessment of patient-reported symptoms and QOL has improved care in a variety of patient populations. Chemotherapy patients randomized to complete PRO assessments at home with nursing alerts for concerning symptoms had fewer emergency room visits, hospitalizations, and better survival [5, 6]. In lung cancer patients, recurrence was detected earlier using PRO monitoring [7]. Few studies have been done using PROs to improve care in thoracic surgery patients specifically. One trial in this group demonstrated postoperative symptom severity decreased using PROs [8]. This proposal aims to build on prior experience with symptom self-reporting by optimizing a thoracic surgery specific patient-reported symptom survey and rigorously testing its implementation. It is a reasonable expectation this patient population will complete the surveys, as they are highly vested in their post-surgical care. In addition, 2 UNC clinics have integrated PROs successfully, and a multitude of UNC research groups with similar patient populations have successfully piloted PRO studies.

Specific gaps in knowledge on PRO use in thoracic surgery have been identified [9, 10]. Barriers include optimal instruments and timing for PRO collection,

utility of PRO monitoring to providers and patients, and association of changes in PROs with postoperative outcomes. To address these issues, this study will evaluate the implementation of PROs for symptom monitoring in thoracic surgery patients and to assess how PROs correlate to readmissions and declines in global QOL. The overall hypothesis of this study is that PROs can be used to identify opportunities for intervention in patients at risk for poor postoperative recovery.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

2.1.1 To determine impact of PRO monitoring with symptom alerts compared to PRO monitoring without symptom alerts after thoracic surgery on post-operative quality of life.

2.1.2 To determine feasibility of 90-day post-operative PRO symptom monitoring after thoracic surgery symptom monitoring eliciting a clinician response.

Feasibility is defined as:

1. $\geq$50% of participants complete all symptom surveys until 3 months post-operatively
2. $\geq$50% of symptom alerts generate a clinician response

2.1.3 To determine barriers/facilitators of PRO monitoring after thoracic surgery through semi-structured interviews of patients and caregivers.

2.2 Secondary Objectives

2.2.1 To determine impact of PRO monitoring with symptom alerts compared to PRO monitoring without symptom alerts after thoracic surgery on post-operative readmission and mortality rates by analyzing:

1. 30-day post-discharge emergency department visit rate
2. 90-day post-discharge emergency department visit rate
3. 30-day post-discharge readmissions rate
4. 90-day post-discharge readmissions rate
5. 30-day mortality (percentage)
6. 365-day mortality (percentage)
7. Change in 2-year quality of life

2.2.2 To determine feasibility of PRO monitoring after thoracic surgery in regards to monitoring long-term quality of life. Feasibility is defined as $\geq$ 50% of patients completing all quality of life surveys at baseline and all follow-up time points.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients participating in PRO monitoring must meet the following inclusion criteria in order to participate in this study:

3.1.1 18 years or older
3.1.2 English speaking
3.1.3 Able and willing to complete web-based symptom survey
3.1.4 Be presenting for elective inpatient thoracic surgery

Caregivers willing to participate in semi-structured interview must meet the following inclusion criteria in order to participate in this study:

3.1.5 18 years or older
3.1.6 English speaking
3.1.7 Be a caregiver for a patient who has undergone thoracic surgery and enrolled in the PRO portion of the study

3.2 Exclusion Criteria

All patients meeting any of the following exclusion criteria at baseline will be excluded from study participation:

3.2.1 Not completing planned surgery within 3 months of obtaining informed consent
3.2.2 Diagnosis of esophageal cancer
3.2.3 Inability to read and speak English
3.2.4 Presenting for day surgery
3.2.5 Presenting for foregut surgery (e.g. paraesophageal hernia repair)
3.2.6 Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
3.2.7 Current incarceration
3.2.8 Pregnancy

Caregivers meeting any of the following exclusion criteria at baseline will be excluded from study participation:

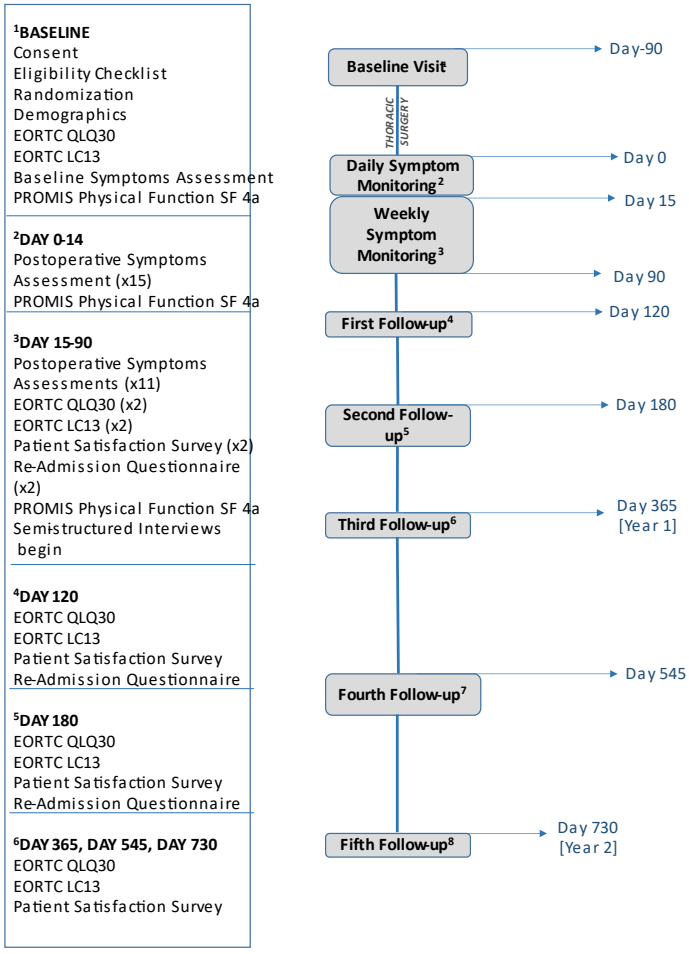
3.2.9 Inability to read and speak English

3.2.10 Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
3.2.11 Current incarceration
3.2.12 Not currently providing care for a patient who has undergone thoracic surgery and enrolled in the PRO portion of the study
3.2.13 Receiving extensive medical treatment (e.g., caregivers admitted in the intensive care unit)

4.0 STUDY PLAN

4.1 Schema

Figure 1: Study Schema



This is a randomized study of 140 participants undergoing thoracic surgery. The primary purpose of this study is to evaluate the implementation of PROs for symptom monitoring in thoracic surgery patients and to assess how management of PROs correlate to readmissions and declines in global QOL. PROs will be administered using the University of North Carolina Patient-Reported Outcomes Core (PRO Core) web-based system. PRO Core maintains a survey system for administering and managing survey reporting. PROs will consist of:

- EORTC QLQ-C30: a cancer-specific survey usable for various cancers
- EORTC QLQ-LC13: a survey used specifically for lung cancer patients
- PROMIS Physical Function SF 4a: a survey used to measure perceived physical mobility and capability
- Pre-operative symptom survey
- Post-operative symptom survey
- Patient Satisfaction survey
- Readmission survey

A subset of 40 patients with varying postoperative experiences and their caregivers will also participate in a semi-structured interview to assess usability and feasibility of the PRO collection.

Patient's active participation is anticipated to last up to approximately 2 years and 3 months. Some patients will have a shortened participation period due to early discontinuation of study procedures.

4.2 Duration of Study

This study will last for approximately 4 years. Up to a total of 140 participants will be enrolled over two years. A subset of approximately 40 patients with varying postoperative experiences and their caregivers will also participate in a semi-structured interview for a total accrual goal of 180 participants. Each patients' participation in the study will last up to 2 years and 3 months. Some patients will have a shortened participation period due to early discontinuation of study procedures. Study analysis of participant data will take place throughout the 4 years.

4.3 Study Details

Participants complete electronic surveys to assess their baseline and post-operative characteristics, symptoms, quality of life, and health outcomes. The study consists of a total number of 9 different surveys.

Figure 2: Survey Frequency and Duration

Survey	Frequency	Completion Time
Pre-operative Symptom Survey	1	5 minutes
Patient Demographics	1	3 minutes
PROMIS Physical Function SF 4a Survey	32	2 minutes
EORTC QLQ-LC13 survey	8	3 minutes
EORTC QLQ-C30 survey	8	8 minutes
Patient Satisfaction survey	7	3 minutes
Readmission Patient Survey	7	2 minutes
Post-operative symptom Daily Survey	15	7 minutes
Post-operative symptom Weekly Survey	11	7 minutes

Enrollment/Baseline Visit

Patients at the multidisciplinary thoracic oncology clinic with plans for thoracic surgery will be approached for enrollment based on inclusion/exclusion criteria described above. An IRB-approved study team member will approach the patient to discuss study procedures, benefits, risks and obtain informed consent prior to any study procedures. The study team member will also teach the patient how to complete the PRO assessment using PRO Core.

At that time, the participant will complete their pre-operative PRO assessment in a private area, which will include PRO surveys as well as demographic questions such as age, sex, and education. PRO survey responses will be reported using the PRO Core database. Paper copies of PRO surveys and source documents will be used if PRO Core system is inaccessible.

For patients who are found to be ineligible during screening or those potentially eligible during screening but found to be ineligible after contact, reasons for ineligibility as well as basic demographics available in the EMR (e.g. race, ethnicity, age, gender, education level if available) will be collected in PRO Core.

For patients who are eligible but refuse enrollment, reasons for refusal, as well as basic demographics available in the EMR (e.g. race, ethnicity, age, gender, education level if available) will also be collected within PRO Core.

Discharge Day (Day 0) Visit:

On the day of discharge (or the next business day in the case of late or weekend discharges), discharge day surveys will be activated in PRO Core by the study staff.

A study team member will call or approach participant in their hospital room before or after discharge to reorient the participant with PRO Core, if needed.

Participants will be reminded of the post-discharge survey schedule, helped with any questions they may have, and assisted with completing any due surveys, if needed.

In the case the day of discharge survey is not obtained (e.g late in the day discharges, weekend discharges, and patient unable or unwilling to complete a survey), this will not be considered a protocol deviation.

The study team member activating the discharge day survey will obtain surgical information from Epic, the surgeon or surgery care team member.

Day 0 (Discharge) to Day 14 Post-Discharge

At this time the following procedures will be performed:

- Daily Post-operative symptom survey
- Daily PROMIS Physical Function SF 4a survey

Day 14 (+/- 7 days) Post-Discharge

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- Patient Satisfaction survey
- Readmission Patient Survey

Day 15 to Day 90 Post Discharge

Weekly symptom monitoring commences. At this time the following procedures will be performed:

- Weekly Post-operative symptom survey
- Weekly PROMIS Physical Function SF 4a survey

Day 60 Post-Discharge (+60 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- Patient Satisfaction survey
- Readmission Patient Survey

Day 120 Post-Discharge (+60 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- PROMIS Physical Function SF 4a survey
- Patient Satisfaction survey
- Readmission Patient Survey

Day 180 Post-Discharge (+185 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- PROMIS Physical Function SF 4a survey
- Patient Satisfaction survey
- Readmission Patient Survey

Day 365 Post-Discharge (+180 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- PROMIS Physical Function SF 4a survey
- Patient Satisfaction survey

Day 545 Post-Discharge (+185 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- PROMIS Physical Function SF 4a survey
- Patient Satisfaction survey

Day 730 Post-Discharge (+185 days)

At this time the following procedures will be performed:

- EORTC QLQ-LC13 survey
- EORTC QLQ-C30 survey
- PROMIS Physical Function SF 4a survey
- Patient Satisfaction survey

Medical chart abstraction will be collected any time after enrollment to capture

clinical events as specified in the protocol.

Semi-Structured Interviews

The PI will identify patients to approach for semi-structured interview. Interviews may also be done with selected participants' caregivers. after the initial participant interviews have been completed. The caregiver interview guide, sampling frame and timeline will be submitted to the IRB once determined. Semi-structured participant interviews will initially be conducted between 14-90 days post-discharge. Sequential interviews will be conducted with the goal to complete10 interview participants in the 14-90 days post-discharge PRO monitoring phase. Once complete or if there are no more participants in the 14-90 days post-discharge phase, the participants will be chosen purposively to capture patients with varying postoperative experiences and low PRO survey completion rates. Patients who completed the 90-days post-discharge symptom surveys but are in long-term follow-up to 12 months post-discharge may also be interviewed to increase the sample size as the study nears the end of enrollment, as needed. Interviews will be administered using interview guides and will continue until thematic saturation is achieved, which will be defined by no new codes being generated to add to the codebook. Semi-structured interview duration is dependent on individual participant responses, but the duration is expected to be approximately 30-60 minutes. The sample size is anticipated to be approximately 40 interviews with patients. An additional 40 interviews will be conducted with selected participants' caregivers for those participants who agree to have caregivers contacted. The participants who are asked to be interviewed will receive a $20 gift card for their participation after completion of the interview.

4.4 Expected Risks

Expected risks for this study are likely minimal and involve psychosocial harms such as emotional distress or embarrassment related to PRO questions and breach of confidentiality. PRO questions are similar to questions used in the clinical setting and therefore are unlikely to cause harm. However, should a patient experience emotional distress stemming from these questions, a psychology consult through the Lineberger Comprehensive Cancer Support Program will be obtained. Risk of confidentiality breach will be minimized in several ways.

Study data will be recorded and stored in PRO Core. UNC PRO Core provides a secure platform for the electronic administration of surveys and collection of data from mobile health devices customized to specific research and clinical care applications. PRO Core data are stored in a secure enterprise-level Oracle database hosted by UNC Center for Bioinformatics, and web servers are also hosted by the UNC Center for Bioinformatics.

Data transmitted between the server and end-users are encrypted using SSL, and all databases are encrypted. Only study team members will have access to data stored in PRO Core, and they will use their ONYEN to log in. Research team

members will be instructed to keep all participant data and patient participation confidential.

Approaching patients about enrollment in the clinic poses a risk to privacy. We anticipate this risk to be low. In the UNC Multidisciplinary Thoracic Oncology Clinic, research teams routinely approach patients for enrollment in clinical studies during clinic, either preceding or succeeding their provider visit. To avoid threats of coercion, providers will be educated but not directly involved with recruitment of patients.

Semi-structured interviews will be conducted by CHAI Core research assistant and/or study team member(s) trained in qualitative interviews. Should participants experience emotional distress related to interview questions, a psychology consult through the Lineberger Comprehensive Cancer Support Program will be obtained. Audio files and word documents containing interview materials will be stored on a secure encrypted server. Recorded interviews will avoid using names (and instead assign codes for each participant) to protect confidentiality. Additionally, if names are inadvertently used during interviews, transcripts will be stripped of participant names. A code key which links the participants interview code to their study ID will be housed separately, on a secure server.

4.5 Removal of Patients from Protocol

Patients will be removed from the study if:

- they experience significant emotional distress in response to PRO surveys
- they indicate that they no longer wish to participate

5.0 TIME AND EVENTS TABLE

5.1 Time and Events Table

Study Procedures	Baseline (-90 days)	Discharge = Day 0 (+ 1 day)	Days 1-6 (+ 1day)	Day 14 (+7 day/+30 days)	Days 8-14 (+ 1day)	Days 21, 28, 35, 42, 49, 56 (+ 7 days)	Day 60 (+ 60 days)	Days 63, 70, 77, 84, 90 (+ 7 days)	Day 120 (+ 60 days)	Day 180 (+ 185 days)	Day 365 (+ 180 days)	Day 545 (+ 185 days)	Day 730 (+ 185 days)
Informed Consent	X												
Eligibility Checklist	X												
Randomization	X												
Participant Demographics	X												
EORTC QLQ30	X			X			X		X	X	X	X	X
EORTC LC13	X			X			X		X	X	X	X	X
Baseline Symptoms Assessment	X												
Postoperative Symptom Assessment (24h recall)		X	X	X	X								
Postoperative Symptoms Assessment (7 day recall)						X		X					
PROMIS Physical Function SF 4a	X	X	X	X	X	X		X	X	X	X	X	X
Patient Satisfaction Survey				X			X		X	X	X	X	X
Re-Admission Survey				X			X		X	X			

Note: Semi-structed interviews will begin after 14 days of discharge

6.0 UNANTICIPATED PROBLEMS

6.1 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.2 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 6.1 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a single center, randomized feasibility study. A total of 140 patients undergoing thoracic surgery will be prospectively enrolled and randomized in a 1:1 ratio. A random block method with blocks of 20 will be utilized to randomize participants to one of two arms to complete PRO (patient reported outcome) symptom monitoring. The two arms are 1) active symptom monitoring and 2) passive symptom monitoring. The participants randomized to active symptom monitoring will have alerts sent to their clinicians when their PRO symptom scores exceed baselines scores by 2 points or more, or when 'severe' or 'very severe' symptoms are reported. Participants randomized to the passive PRO monitoring arm will complete the same PROs as participants in the active monitoring arm, but will not have alerts sent to their clinician. All participants will be administered survey instruments to further assess quality of life including: EORTC QLQ30, EORTC LC13, PROMIS Physical Function SF 4a survey SF 4a. Additionally, in order to assess the feasibility of the PRO monitoring system, all participants will be asked to complete a Patient Satisfaction survey. In addition, a subset of 40 participants and 40 caregivers will be chosen to complete a semi-structured interview, if willing, to assess patient satisfaction with symptom monitoring experience. The subset will be made up of a range of post-operative experiences and will be a fair representation of study population, including both

study arms. Participants will be chosen by principal investigator and eligible to participate in interview after 14 days of discharge

The primary objectives are to determine 1) impact of PRO monitoring with symptom alerts compared to PRO monitoring without symptom alerts after thoracic surgery on post-operative quality of life 2) feasibility of 3-month post-operative PRO symptom monitoring after thoracic surgery symptom monitoring eliciting a clinician response 3) barriers/facilitators of PRO monitoring after thoracic surgery through semi-structured interviews of patients.

Secondary objectives include: 1) determining impact of PRO monitoring with symptom alerts compared to PRO monitoring without symptom alerts after thoracic surgery on post-operative readmission and mortality rates 2) determining feasibility of PRO monitoring after thoracic surgery in regards to monitoring quality of life.

7.2 Sample Size and Accrual

We originally anticipated 100-150 patients to be enrolled per year. A sample size of 66 in each group will have 80% power to detect a difference in mean EORTC scores of 10.000 assuming that the common standard deviation is 22.900 using two group t-test with a 0.050 one-sided significance level. The target sample size was 140 patients to allow appropriate block randomization in groups of 20. Based on enrolling about 140 patients, we would be powered to detect an effect size of 0.437 (difference in means of 10, common standard deviation of 22.9). Due to slower accrual in context of COVID-19, we anticipate enrollment of 100-140 patients before funding ends. With 100 patients, we will have 80% power to detect an effect size of 0.501 (difference in means of 11.467, common standard deviation of 22.9). Power calculations were performed using SAS version 9.4 (SAS Inc., Cary, NC) using PROC POWER and a two sample means difference test.

7.3 Data Analysis Plans

7.3.1 Aim 1: Impact of PRO monitoring with symptom alerts, compared to PRO monitoring without alerts, after thoracic surgery on post-operative quality of life.

Impact will be determined by comparing baseline quality of life to quality of life at the following timepoints: Day 14, Day 60, Day 120, Day 180, and Day 365 post-discharge. QOL will be measured by administering European Organisation for Research and Treatment of Cancer's (EORTC) EORTC QLQ-LC13 and EORTC QLQ-C30. These surveys will be scored according to methods described in the EORTC scoring manual: https://qol.eortc.org/manual/scoring-manual.

Student's T and/or Wilcoxon rank sum tests will be used to perform bivariable comparisons of EORTC scores at each of the time points (baseline/pre-operative and Day 12, Day 60, Day 120, Day 180, and Day 365 post-operative).

Additionally, a linear mixed effect model will be used to assess the average

change in EORTC scores over time amongst both groups, and the difference in average trajectory between them, after accounting for repeated measures and within- and between- subject variability. Both a random intercept and slope (for time) statement will be used, and an unstructured correlation matrix will be applied. The random intercept and slope will allow us to assess the impact of symptom alerts while allowing for random variation in baseline quality of life and trajectories.

If there are convergence issues, simpler correlation structures may be used (e.g. independent) or the random slope parameter may be dropped. Dropping the random slope parameter will mean we are assuming that there is no/minimal individual variation in trajectory across patients.

7.3.2 Aim 2: Determine feasibility of 3-month post-operative PRO symptom monitoring with alerts.

The proportion of completed symptom surveys (overall and in each arm) at 3-months postoperative will be calculated, as well as the proportion of participants who completed all surveys during that time. Chi-square, Student's T, and Wilcoxon rank sum tests will be used to compare patient demographics, study arm, and surgery characteristics between those who did and did not complete all surveys to attempt to identify predictors of compliance. Multivariable logistic regression may also be used.

Similar methods will be used to assess proportion of symptom alerts that generate a clinician response.

7.3.3 Aim 3: Identify barriers/facilitators of PRO monitoring through semi-structured interviews.

Patient and caregiver interview transcripts will be analyzed as they are collected. Transcripts will be coded using in vivo coding methods and a code book will be created. Interviews will continue until thematic saturation is achieved, which will be defined by no new codes being generated to add to the code book.

7.3.4 Sub-Aim 1: Impact of PRO monitoring with symptom alerts, compared to PRO monitoring without symptom alerts, on post-operative readmission and mortality rates.

Kaplan Meier curves and Cox proportional hazards regression will be used to assess the impact of study treatment arm on 30-day and 90-day emergency department (ED) visits, readmissions, and all-cause mortality, as well as 1-year all-cause mortality. A linear mixed effect model will be used to assess the change in 2-year quality of life (described in Aim 1).

Patients who are lost to follow-up will be censored at their last clinician/study interaction. Mortality will be treated as a competing risk for ED visits and readmission. This aim will be approached as an intent-to-treat analysis and will not require that patients used their PRO monitoring or had symptom alerts sent to

their clinician.

7.3.5 Sub-Aim 2: Determine the feasibility of PRO monitoring for assessing quality of life.

Similar methods to Aim 2 will be used. The proportion of completed QOL surveys (overall and in each arm) at each time point (baseline/pre-operative and 2-weeks, 6-months, 1-year, and 2-year post-operative) will be calculated, as well as the proportion of participants who completed all surveys during that time. Chi-square, Student's T, and Wilcoxon rank sum tests will be used to compare patient demographics, study arm, and surgery characteristics between those who did and did not complete all surveys to attempt to identify predictors of compliance. Multivariable logistic regression may also be used.

7.4 Data Management/Audit

PRO data will be collected and managed via PRO-Core's web-based administration systems. Satisfaction survey data will also be entered into the PRO-Core database via web-based administration. Abstracted medical record data will be entered into a PRO-Core study-specific database. PRO-Core employs a secure enterprise-level Oracle database managed by the ITS Research Computing group at UNC, and web servers are hosted by the UNC Center for Bioinformatics. Data transmitted between the server and end-users are encrypted using SSL, and all databases are encrypted.

CHAI Core and/or TS-PRO study team member(s) trained in qualitative interview will conduct all semi-structured interviews with patient and caregiver participants. Each interview will be audio recorded digitally and transcribed verbatim. The interview recordings and transcripts will be stored in a study-specific password-protected folder.

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC) as required.

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc. and the team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

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.

8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Office of Clinical & Translational Research (OCTR) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol
- A copy of the IRB approved consent form

8.3 Registration Procedures

All subjects must be registered with the Lineberger Comprehensive Cancer Center, and entered into the web based clinical research platform, Oncore®. Patient enrollment will also be documented in a password protected excel spread sheet stored on a shared drive managed by Lineberger Comprehensive Cancer Center's encrypted server.

8.4 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.

8.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification

form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.4.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review. Participant-initiated changes from recommended symptom monitoring schedule (ie- non-adherence) will not be considered protocol deviations. A protocol deviation would only be recorded if the staff and its systems (i.e. PRO Core) did not initiate/reach out to patients to administer the appropriate surveys or deliver appropriate alerts.

Events will be documented in OnCore, but not reported to the IRB unless it is due to a related AE or SAE. UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO): Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 6.1) must be reported by the Study Coordinator using the IRB's web-based reporting system.

8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. 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.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.6 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 all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two 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 three years after the completion and final study report of this investigational study.

8.7 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.

9.0 REFERENCES

1. Cykert, S., G. Kissling, and C.J. Hansen, Patient preferences regarding possible outcomes of lung resection: what outcomes should preoperative evaluations target? Chest, 2000. 117(6): p. 1551-9.
2. Pompili, C., et al., Predictors of post-operative decline in quality of life after major lung resections. Eur J Cardiothorac Surg, 2011. 39(5): p. 732-7.
3. Billmeier, S.E., et al., Predictors of nursing home admission, severe functional impairment, or death one year after surgery for non-small cell lung cancer. Ann Surg, 2013. 257(3): p. 555-63.
4. Stiles, B.M., et al., Incidence and Factors Associated With Hospital Readmission After Pulmonary Lobectomy. Ann Thorac Surg, 2016. 101(2): p. 434-42; diacussion 442-3.
5. Basch, E., et al., Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA, 2017. 318(2): p. 197-198.
6. Basch, E., et al., Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol, 2016. 34(6): p. 557-65.
7. Denis, F., et al., Improving Survival in Patients Treated for a Lung Cancer Using Self-Evaluated Symptoms Reported Through a Web Application. Am J Clin Oncol, 2017. 40(5): p. 464-469.
8. Cleeland, C.S., et al., Automated symptom alerts reduce post-operative symptom severity after cancer surgery: a randomized controlled clinical trial. J Clin Oncol, 2011. 29(8): p. 994-1000.
9. Pompili, C., et al., Patients reported outcomes in thoracic surgery. J Thorac Dis, 2018. 10(2): p. 703-706.
10. Subramanian, M., et al., Patient Reported Outcomes in Cardiothoracic Surgery. Ann Thorac Surg, 2018.
11. Lamas, D.J., et al., Looking beyond Mortality in Transplantation Outcomes. N Engl J Med, 2018. 379(20): p. 1889-1891.
12. Cykert, S., et al., Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. JAMA, 2010. 303(23): p. 2368-76
13. Cykert, S. and N. Phifer, Surgical decisions for early stage, non-small cell lung cancer: which racially sensitive perceptions of cancer are likely to explain racial variation in surgery? Med Decis Making, 2003. 23(2): p. 167-76.
14. Reeve, B.B., et al., Impact of cancer on health-related quality of life of older Americans. J Natl Cancer Inst, 2009. 101(12): p. 860-8.
15. Jean, R.A., et al., When good operations go bad: The additive effect of comorbidity and post-operative complications on readmission after pulmonary

lobectomy. Surgery, 2018. 164(2): p. 294-299.
16. Khullar, O.V., et al., Pilot Study to Integrate Patient Reported Outcomes After Lung Cancer Operations Into The Society of Thoracic Surgeons Database. Ann Thorac Surg, 2017. 104(1): p. 245-253.
17. Moller, A. and U. Sartipy, Long-term health-related quality of life following surgery for lung cancer. Eur J Cardiothorac Surg, 2012. 41(2): p. 362-7.
18. Rizk, N.P., et al., A prospective trial comparing pain and quality of life measures after anatomic lung resection using thoracoscopy or thoracotomy. Ann Thorac Surg, 2014. 98(4): p. 1160-6.
19. Cykert, S., et al., Weighing projections of physical decline in lung cancer surgery decisions. Am J Med Sci, 2015. 349(1): p. 61-6.
20. Basch, E., et al., Development of the National Cancer Institute's patient-reported outcomes version of
the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst, 2014. 106(9).
21. Basch, E., et al., Feasibility of Patient Reporting of Symptomatic Adverse Events via the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in a Chemoradiotherapy Cooperative Group Multicenter Clinical Trial. Int J Radiat Oncol Biol Phys, 2017. 98(2): p. 409-418.
22. Pusic, A.L., et al., Patient-reported outcome measures in plastic surgery: use and interpretation in evidence-based medicine. Plast Reconstr Surg, 2011. 127(3): p. 1361-7. Mody, Gita

10.0 APPENDICES (See Attached)

- Pre-operative Symptom Survey
- Participant Demographics Form
- Refusal/Ineligible demographics from
- Post-operative Symptom Daily Survey
- Post-operative Symptom Weekly Survey
- Quality of Life Surveys: EORTC QLQ30 & EORTC LC13
- PROMIS Physical Function SF 4a Survey
- Readmission Patient Survey
- Patient Satisfaction Survey
- Caregiver Interview Guide
- Participant Interview Guide