PROTOCOL AMENDMENT #4

FEASIBILITY AND ACCEPTABILITY OF REMOTE MONITORING OF LUNG CANCER PATIENT-REPORTED OUTCOMES USING MOOVCARE®

AMENDMENT INCORPORATES (check all that apply):

x Editorial, administrative changes
x Scientific changes
x Therapy changes
x Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

The purpose of this amendment is to update secondary and exploratory endpoints and make administrative changes. The sponsor has asked for these changes.

The following changes have been made to the protocol:

Section 1.1	Updated target population and study participation duration
Section 2.0	Updated secondary and exploratory endpoints
Section 4.1	Updated study schema, changed study participation duration, updated timepoints for patient and provider satisfaction surveys
Section 4.2	Updated study duration, enrollment period, and accrual goal
Section 4.3	Updated unattended alerts escalation process, and outcome surveys timepoints
Section 5.1	Updated time and event table to reflect the change in the study participation duration and updated survey frequency
Section 7.1	Clarified primary objective
Section 7.2	Updated sample size and accrual duration
Section 7.3	Updated post-baseline assessment time point under supplemental analysis to remove the time points after 6 months.
Section 7.5	Updated language on AE and SAE collection and reporting and updated unattended alerts escalation process

THE ATTACHED VERSION DATED APRIL 19, 2022 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF THE PROTOCOL

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

FEASIBILITY AND ACCEPTABILITY OF REMOTE MONITORING OF LUNG CANCER PATIENT-REPORTED OUTCOMES USING MOOVCARE®

Principal Investigator
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[redacted]

Sponsor: Sivan Innovation

Funding Source: Sivan Innovation

Version Date: 19April2022

FEASIBILITY AND ACCEPTABLITY OF REMOTE MONITORING OF PATIENT-REPORTED SYMPTOMS IN LUNG CANCER PATIENTS USING MOOVCARE®

Principal Investigator
Gita Mody, MD, MPH
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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_____

PI signature: *via IRBIS certification*

Version Date: 19April2022, Protocol Amendment 4

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This single site study is being conducted to evaluate the feasibility and acceptability of monitoring lung cancer patients' disease- and therapy-related symptoms remotely with electronic patient-reported outcome (ePRO) surveys. Up to 50 patients undergoing treatment and/or surveillance for new or existing diagnoses of lung cancer at the University of North Carolina's Lineberger Comprehensive Cancer Center will be prospectively enrolled to the use of the mobile medical application Moovcare® for 6 months. Moovcare® automatically delivers ePRO surveys on common symptoms experienced by lung cancer patients. Results are stored in a secure web-based portal for provider review. Concerning survey responses are reported to a designated provider via an email alert.

This study will evaluate and report on: patient adherence with surveys, patient and provider satisfaction with Moovcare®, quality of life, and survival during the study period.

1.2 Background

In the United States, lung cancer was the third most commonly diagnosed cancer (>200,000 cases) and the leading cause of cancer death (>140,000 fatalities) in 2019.[1,2] While the majority of lung cancer patients are at an advanced stage at presentation and survival is still less than 20% at 5 years,[1] increasing numbers of patients are living longer due to advances in chemotherapy and immunotherapy regimens. Lung cancer patients are highly symptomatic due to the tumor itself and the side effects of multimodal therapy.[3] Therefore, strategies for systematic outpatient symptom monitoring that lead to earlier clinician management before symptoms become severe and lead to emergency department visits, hospitalizations, or other complications are anticipated to be clinically meaningful in this group.

Electronic patient-reported outcome (ePRO) surveys can be used to monitor symptoms related to disease and treatment remotely in ambulatory patients. ePRO monitoring systems automatically deliver surveys that capture symptoms directly from patients and alert providers in real-time to concerning responses above predetermined symptom severity thresholds. ePRO monitoring has been shown to result in improvement of routine clinical care in the oncology population. In a large randomized controlled trial of advanced cancer patients, ePRO monitoring was associated with reduced emergency department (ED) visits and hospital readmissions, improved quality of life (QOL) and patient satisfaction, and increased overall survival, findings supported by other studies.[4-7]

Moovcare® is a web-mediated ePRO survey delivery and monitoring system designed for the detection of recurrent lung cancer. Patients are automatically

reminded through emails to complete weekly surveys on symptoms common to lung cancer patients. Providers are notified for concerning changes in symptoms based on a previously validated algorithm predictive of lung cancer recurrence.[8] In prior studies, lung cancer recurrence in patients with advanced lung cancer was detected earlier and survival was improved in patients using Moovcare®. [8,9]

1.3 Purpose and Rationale

The purpose of this study is to demonstrate the feasibility and acceptability of using Moovcare® to monitor symptoms related to complications of treatment (surgery, radiotherapy, and/or chemotherapy) and disease recurrence in American lung cancer patients as well as to provide preliminary data to inform future controlled studies on the association of ePRO monitoring with clinical and quality of life outcomes.

The study of the implementation of mobile health information technology (HIT), such as Moovcare®, in diverse patient populations and settings is important to identify and solve barriers to uptake. This study will endeavor to show feasibility of ePRO HIT in patients receiving care at the University of North Carolina (UNC), a large public, academic hospital setting. In a separate UNC study looking at the feasibility and impact of ePRO monitoring for the initial 90 days after discharge from thoracic surgery (including lung resection for cancer), initial study experience suggests ePRO use is likely to be feasible in other patients with intrathoracic pathology including lung cancer patients. Evaluating compliance with longitudinal ePRO monitoring throughout the treatment and surveillance periods of lung cancer patients will allow protocols for use in multidisciplinary care to be developed.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

2.1.1 The primary objective of the study is to evaluate the feasibility of self-reporting symptoms by lung cancer patients using Moovcare®. Feasibility will be defined as the mean of assigned weekly ePRO surveys completed per patient.

2.1.2 The primary endpoint will be:

1. ePRO survey completion rate: the mean percentage of surveys completed per patient by 6 months or coming off study per protocol if sooner.

2.2 Secondary Objectives

The secondary objectives of the study will be to evaluate the acceptability of Moovcare® (through patient and provider satisfaction surveys) and estimate the overall survival and change in the quality of life in patients using Moovcare®.

2.2.1 Secondary Endpoints will be:

1. Percentage of patients surveyed at 6 months on study satisfied with care team communication.
2. Health-related quality of life (HRQOL): change in comprehensive EORTC-QLQ30 and LC13 survey score from baseline at 6 months.
3. Overall Survival (from time of enrollment).
4. Percentage of surveys completed at each weekly delivery time point

2.2.2 Exploratory endpoints will be:

1. [redacted]

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients participating in the study must meet the following inclusion criteria at baseline:

3.1.1 18 years or older
3.1.2 Diagnosis of lung cancer (any histology, any stage) undergoing outpatient treatment and/or surveillance/monitoring at UNC.

This may include stage I and II patients who have completed lung resection and/or are undergoing radiation, stage II and III patients receiving neoadjuvant, adjuvant, or definitive chemotherapy, stage IV patients undergoing active therapy or monitoring, patients undergoing surveillance for treated or untreated stage I-III lung cancer, and both limited and extensive small cell lung cancer. The study team will request confirmation of the lung cancer diagnosis from the managing clinician. Patients can be enrolled at any point in their lung cancer treatment trajectory (i.e., not just at initiation of first-line treatment) after a diagnosis of lung cancer has been assigned by the treating clinician. This may include patients assigned a diagnosis of lung cancerwithout a tissue diagnosis.

3.1.3 Speaks and understands English
3.1.4 Reliable access to the internet and email
3.1.5 Access to a mobile phone (or device that can receive text messages for registration)

3.2 Exclusion Criteria

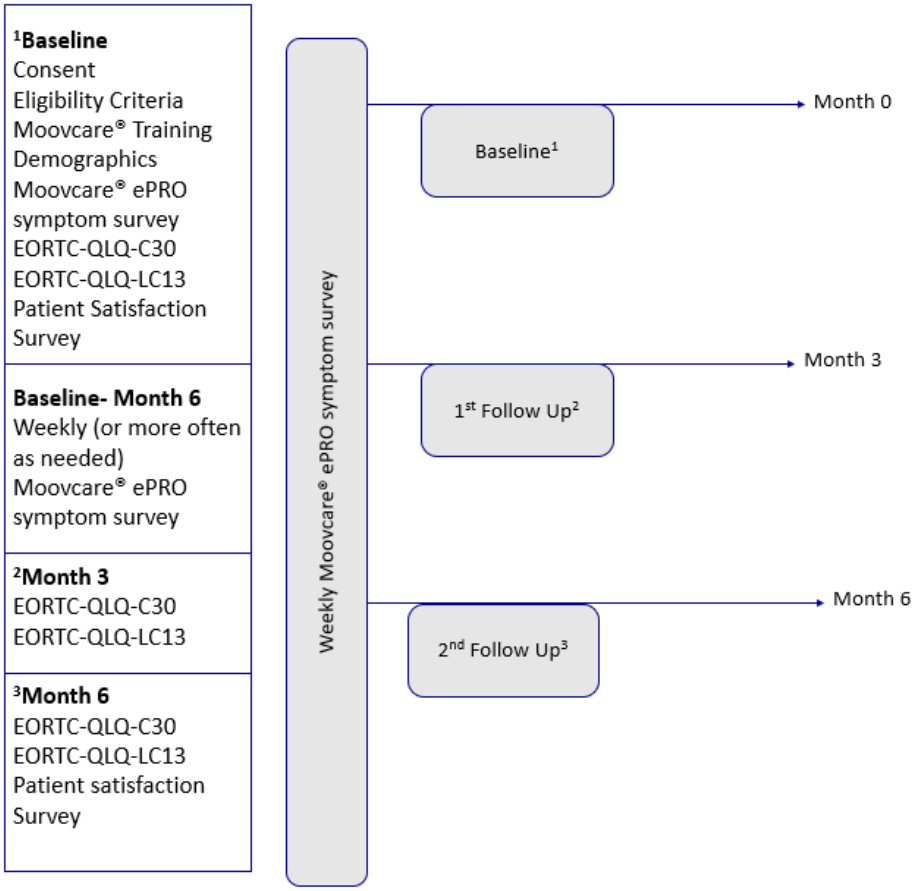
All participants meeting any of the following exclusion criteria at baseline will be excluded from study participation:

3.2.1 Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing study procedures
3.2.2 Current participation in other PRO monitoring trials
3.3.3 Inability to read and speak English
3.3.4 Current incarceration

4.0 Study plan

4.1 Schema

Figure 1: Study Scheme



This is a single site nonrandomized feasibility study of approximately 50 participants on treatment and/or surveillance for new or existing diagnoses of lung cancer who will be assigned to a single-arm involving monitoring of their patient-reported outcomes using a mobile medical application. The study population will include patients with a diagnosis of lung cancer undergoing outpatient treatment or

surveillance at UNC. Patients will be recruited from the Multidisciplinary Thoracic Oncology Program (MTOP) clinics at UNC over 10-12 months and undergo ePRO monitoring for 6 months or until criteria for coming off study are met, whichever comes first. Study procedures include monitoring of patient symptoms using automated weekly PRO surveys delivered by Moovcare® and assessment of outcomes including quality of life at baseline and 3-month intervals, as well as patient satisfaction at 6 months using the UNC REDCap electronic survey delivery software platform. Other clinical outcomes including health care utilization, recurrence, and survival will be abstracted at any time after enrollment from the medical record into the UNC REDCap database. Provider satisfaction will be assessed via electronic survey after the study has been open to enrollment for at least 6 months.

4.2 Duration of Study

This study will last for approximately 2 years. Training of providers will take place prior to enrollment starts. Approximately 50 participants will be enrolled over 1 year. Each participants' participation in the study will last up to 6 months or until the patient comes off-study due to transition to hospice, death, or withdrawal from the study. Study analysis of participant data will take place throughout the study duration and at the conclusion.

4.3 Study Details

Overview

The study involves two types of repeating surveys: weekly PRO surveys delivered by e-mail via Moovcare® and periodic outcomes surveys delivered by e-mail via the UNC REDCap platform, a secure web-based server, or collected on paper in the clinic. PRO responses are managed by providers through a combination of reports graphically displaying responses over time and e-mail alerts about concerning levels or combinations of symptoms. Provider response to ePRO reports and alerts may lead to earlier or different management than routine clinical care and so potentially impact health care utilization and clinical outcomes. For all surveys (Moovcare® PRO and REDCap outcome surveys), participants' caregivers (family, friends) may assist with completion in any way the participant chooses. The study coordinator may also provide technical assistance.

Screening, Recruitment, and Enrollment

Potentially eligible patients will be identified from the review of the visit reason fromthe thoracic oncology providers' Epic clinic schedules. Patients who have appointments for outpatient care at Multidisciplinary Thoracic Oncology Program (postoperative clinic visit, any radiation, or oncology visit) will be considered. To identify potentially eligible patients, the study coordinator can review clinical documentation such as the patient's chart in the electronic medical record, clinical schedules, or ask clinical staff about potential eligible patients through a limited HIPAA waiver from the IRB. Providers will also be approached by the study coordinator to identify any other patients with lung cancer.

Identified patients will be entered into a screening log. Providers will be asked to verify a clinical diagnosis of lung cancer. For surgical patients, lack of enrollment in concurrent LCCC protocol #1945 will be verified with the assigned study coordinator. Patients meeting the eligibility criteria on the initial screening will be approached in person, by telephone by the study coordinator to verify the remainder of the eligibility criteria and invite the patient to the study. Interested patients will undergo informed consent procedures. 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. Patients who agree to participate will review and sign the informed consent form after the study is explained and questions have been answered.

Patients who are found to be ineligible during screening due to lack of email, phone number, or English language or those potentially eligible during screening but found to be ineligible after contact will be excluded from the study. The reasons for exclusion as well as basic demographics available in the EMR (e.g. race, ethnicity, age, gender, education level if available) will be collected in REDCap.

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 REDCap.

Moovcare® Registration and Use

After enrollment, participants will be registered and receive a log-in ID for the Moovcare® website. Participants will be trained by the study coordinator on the purpose of ePRO monitoring and how to log in and self-report PROs using the Moovcare® application. Participants will be instructed that any time a severe or worsening symptom is reported, their care team will be alerted but that the alert will only be received during business hours. If there is a severe symptom warranting attention outside of business hours, participants will be instructed to contact the care team directly or visit the emergency room. Participants should be informed that this system cannot be counted on as the sole means of communicating problems to their care team, and that any time a concerning symptom occurs, they should consider contacting a health care provider or calling 911 as they would do if participating in the study.

The Moovcare® survey system asks questions about common symptoms lung cancer patients experience, specifically about loss of weight, loss of appetite, dyspnea, depression, cough, pain, fever, hemoptysis, subcutaneous nodules, dysphonia, and superior vena cava syndrome.

The Moovcare® application will notify the patient via email on a weekly basis during daytime hours to complete a scheduled symptom survey within 24 hours. If the patient does not complete the scheduled Moovcare® survey by the deadline, the system will generate e-mail reminders. If the survey is not completed after 48-72 hours, the study coordinator may also contact patients for a reminder. Participants

will have the option to report symptoms via Moovcare® more often as needed.

Before study initiation, the study coordinator will train all providers on the MTOP team on use of the Moovcare® portal, intended use of ePROs for symptom monitoring and management, and logging on and viewing ePRO results in the portal between and during clinic visits. Providers will also be trained on the need to document management of ePRO symptoms in the regular medical record (i.e. Epic) per service routine.

Provider Alerts and Reports

Members of the MTOP care team(s) will be assigned to each participant within the Moovcare® portal. ePRO survey symptoms that are severe and/or meet the Moovcare® algorithm for lung cancer recurrence prediction will generate an email alert to a designated clinical care team member. Any free text addressing "other" symptoms will also generate an email alert. The care team will follow their usual protocols for management of symptoms which may include calling patient for more information or to manage the issue, scheduling an appointment or testing, and/or referring to the emergency room amongst other management strategies. At any time, the MTOP care team members can review an assigned participant's record to determine whether an alert is present and to review the prior ePRO symptom survey responses. If the providers did not view the alert in 48 hours, patients will get a message to contact their health care provider. The unattended alerts will also be escalated to the research coordinator who will communicate it with the clinical team. The study coordinator will have access to all enrolled participants' Moovcare® records to facilitate review of results.

Outcome Surveys

At enrollment, all participants will be trained by the study coordinator how to use the UNC REDCap online system to complete outcomes surveys for the trial. The outcomes surveys will be completed by all participants at baseline; HRQOL will be reassessed at months 3, 6/off-study (+/- 4 weeks each) and patient satisfaction at 6 months/off-study (+/-4 weeks). Participants will be given a choice to complete from home electronically, or if necessary, in clinic at otherwise scheduled routine follow-up visits which occur at least every 3 months or via phone call (with the study coordinator entering the data after participant paper completion into REDCap). For home electronic completion, the outcomes surveys will be sent when due by email via REDCap. The REDCap will send automatic reminders for incomplete surveys. If the patient does not self-complete this information, the study coordinator also has the option to call or email them to collect the information and then enter it into REDCap. If the patient goes off study prior to week 26, the study coordinator will contact the patient as soon as possible to get the off-study surveys completed.

The patient outcomes surveys include:

- **Participant Demographics Form:** This form asks participants about their baseline information including full name and date of birth and will be administered at the time of enrollment.
- **Quality of Life Questionnaires:** Health-related quality of life will be

assessed by items from the *European Organisation for Research and Treatment of Cancer* Quality of Life Questionnaire Comprehensive 30 (EORTC-QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 module (EORTC-QLQ-LC13), which will be administered to each patient participant at baseline, months 3, 6/off- study (+/- 4 weeks each). The EORTC is a well-established and frequently used questionnaire that includes a 5-item physical functioning domain, individual symptom items including symptoms specific to lung cancer patients, and a composite quality of life score.

- **Patient Satisfaction Survey:** The patient satisfaction survey will be administered to each participant at baseline and 6 months of participation (+/- 4 weeks). The satisfaction questions are from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey system, which is maintained by the Agency for Healthcare Research and Quality (AHRQ), to support and promote the assessment of consumers' experiences with health care, and from the "Patient-Centered Communication in Cancer Care" short form and validated instrument (PCC-CA-6). No total score is calculated, but individual items will be summarizedand reported.

Chart Abstraction Form

The study coordinator will abstract information from the medical chart and/or touch base with the clinical team caring for participants to assess clinical outcomes including if the patient has died, been hospitalized or admitted to the emergency department or urgent care, or had recurrence, progression, or death at any time after enrollment and at off study. This form will collect relevant medical information, including dates and diagnoses related to ER visits and hospitalizations, prescription of selective supportive medications, dates of changes and/or discontinuation of cancer treatments, and initiation of hospice services.

Provider Satisfaction Survey

The amount of staff effort for PRO-related activities will be assessed based on data completed by the MTOP nurses and physicians involved in managing PRO data. The provider satisfaction survey will be completed at least 6 months from the time the initial participant is enrolled. The study coordinator will ask the providers to complete the form on paper and then immediately upload the results into REDCap or directly enter survey results into REDCap by tablet or computer emailed survey link. The provider survey satisfaction may be repeated during the study duration particularly if changes to the Moovcare® interface or protocol are made.

Off-Study Timing and Procedures

Participants are asked to remain on the study completing surveys for 6 months (26 weekly ePROs), or until they go off-study prior to that time. An "Off-study form" requiring information to be abstracted from the participant's medical record will be completed by the study coordinator when the participant goes off study (+ 4-week window for form completion). Consultation with MTOP physician or nurse may be necessary for clarifications of some of the questions in

this form. For example, this form includes information about reasons and timing for the reasons for going off-study. In addition, the final chart abstraction form will also be completed (see above) when going off study. In addition, if a patient goes off study early for any reason other than death, the coordinator will attempt to contact the patient to complete the final Outcomes Questionnaires (including: "Patient Quality of Life" and "Patient Satisfaction") as soon as possible.

Some of the reasons for patients going off-study include:

- Completion of 6 months (26 weeks) of participation
- Initiation of hospice
- Death
- Moved to a different practice for lung cancer care
- Voluntary disenrollment
- Lost to follow-up
- Removal by principal investigator

Incentives

Participants will be informed at the time of recruitment they will be given a $25 incentive for participation (at enrollment in the Moovcare® portal).

4.4 Expected Risks

Expected risks for this study are likely minimal and involve psychosocial harms such as emotional distress or embarrassment related to survey questions and breach of confidentiality. Survey 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 as detailed below:

1. Moovcare® is a web-mediated algorithm where patients enter symptom data through a password-secure web platform. Enrolled participants are given a unique password to log on to the site so only they, a caregiver with whom they share the password, and their assigned clinical care team can access their PRO data. Other study data including outcomes questionnaires and chart abstraction forms will be collected through the University of North Carolina (UNC) REDCap web-based platform for secure survey administration.
2. The REDCap system is a secure, HIPAA-compliant web-based application to support distributed data collection governed by standard University, School ofMedicine, and Federal information security policies and standards. The REDCap application is hosted and monitored on a secure server located within the UNC CTSA-funded NC TraCS Institute's Bioinformatics Core. Access to the REDCap database for this study will be restricted to authorized research team members as needed to perform their job functions. Research staff who access the REDCap system will use a unique user ID

provided by the Bioinformatics Core. Each time research staff access REDCap, a unique username and password (login) is required, and REDCap maintains an audit trail of all activity.

3. Strict confidentiality will be maintained. Hard-copy research data will be minimal and stored in locked, secure areas accessible only by the study team. Research data will be maintained in separate charts and identified by ID number only when possible. A master list connecting names and ID numbers will be kept in a separate, secure location. Only IRB-approved members of theresearch team will have access to secured files and will be educated regardingthe protection of patients' rights to confidentiality. At study completion, when the database has been declared to be complete and accurate, the database will be locked.
4. Data transmitted between the server and end-users are encrypted using SSL, and all databases are encrypted. Only study team members will have access todata stored in REDCap, and they will use their UNC ONYEN to gain access. Research team members will be instructed to keep all participant data and patient participation confidential.
5. Approaching patients about enrollment in the clinic poses a risk to privacy. We anticipate this risk to be low. To avoid threats of coercion, providers willbe educated but not directly involved with recruitment of patients.

4.5 Removal of Patients from Protocol

Patients will be removed from the study if:

- they experience significant emotional distress in response to mobile remote monitoring
- they indicate that they no longer wish to participate

5.0 TIME AND EVENTS TABLE

5.1 Time and Events Table

The study procedures by each study timepoint are detailed below:

Enrollment/Baseline Visit
At this time, the following procedures will be performed:

- In person/telephone recruitment and consent
- Registration and training on Moovcare®
- Patient Demographic Form
- Quality Life Surveys and Patient satisfaction survey (*if in person recruitment and/or enrollment, the participant will complete their baseline survey assessment in a private area of the clinic with study coordinator assistance)*

Weekly (0-6 months as needed)

At this time, the following procedures will be performed:

- Moovcare® ePRO symptom survey

Month 3, 6/off study

At this time, the following procedures will be performed:

- Patient Quality of Life Survey

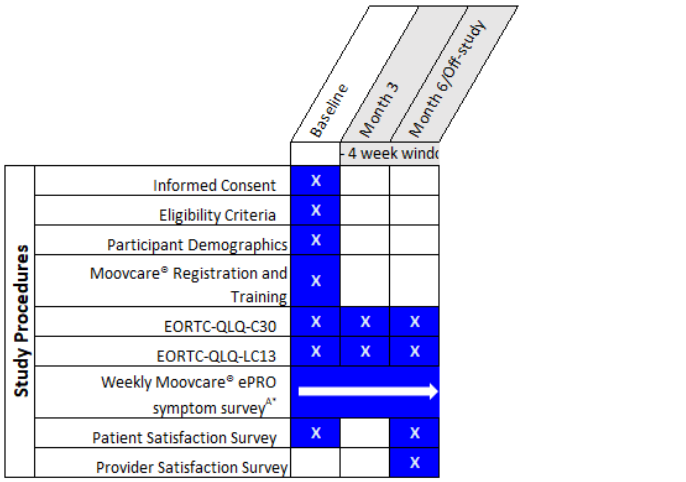
Month 6/off study

At this time, the following procedures will be performed:

- Patient Satisfaction Survey

Medical chart abstraction will be conducted at any time after enrollment and at off study.

Schedule of Activities:



*Participants may also complete the Moovcare® ePRO symptom survey on an as needed basis

Survey Frequency and Duration:

Survey	Frequency	Completion Time
Patient Satisfaction Survey	2	3 minutes
EORTC QLQ-C30 survey	3	10 minutes
EORTC QLQ-LC13 survey	3	4 minutes
Weekly Symptom Survey	26	7 minutes
Patient – Initiated Symptom Survey	As needed	7 minutes

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 nonrandomized, single-center, interventional study. The project will prospectively enroll eligible lung cancer patients undergoing outpatient treatments to a single arm entailing monitoring with weekly patient-reported outcomes surveys linked to automated provider reporting. Outcomes will be measured serially over the course of the study using surveys and chart abstraction.

The primary objective of this study is to evaluate feasibility, acceptability, and adherence with survey completion at the patient level. Secondary objectives include estimating the overall survival and change in quality of life in patients using Moovcare®.

7.2 Sample Size and Accrual

The primary objective is to estimate the percentage of available surveys completed by eligible, enrolled patients. Based on other PRO studies including at UNC, approximately 80% of assigned surveys are completed per patient.

The Multidisciplinary Thoracic Oncology Program (MTOP) at the UNC Lineberger Comprehensive Cancer Center sees a patient population representation of the state of North Carolina including approximately 20% African American and 60% female patients. An estimated 600 patients with lung cancer diagnoses are seen each year. Based on other studies on PROs at UNC institutions, it is estimated that 50% of patients meeting screening criteria will be otherwise eligible and enroll., It will take an anticipated 12 months to enroll the target of 50 patients.

7.3 Data Analysis Plans

Primary data analysis will include the average per patient survey completion rate, change in quality of life, and patient satisfaction at 6 months.

Descriptive statistics will be provided for patient and provider satisfaction scores. Overall survival will be calculated using the Kaplan Meier method, with time starting at enrollment, and ending at last contact or date of death.

Changes in HRQOL, as measured by the EORTC-QLQC30, from baseline to 6 months will be calculated and tested using a paired t-test. Sensitivity analyses will be done using last observation carried forward from 3 months if the 6-month surveys is not answered. If a patient dies before the endpoint of 6 months, they will not be included in these estimates. Longitudinal modeling, including all data over the year, will also be explored to further investigate changes over time.

Exploratory Analyses:
Exploratory data analysis will include comparison of demographics of participants completing most (>75%) of the PRO surveys to those not completing most of the PRO surveys using Chi-squared tests for categorical variables and t-tests for continuous variables. Additional comparisons will be done of available demographics of patients (self-reported or obtainable with a limited HIPAA authorization waiver by the IRB) who refuse enrollment and ineligible patients due to key inclusion criteria such as access to email compared to enrolled patients.

Survival curves will be compared for patients with varying levels of PRO survey compliance (no surveys, >=1 survey, >=75% surveys completed) using a landmark analysis based on the first month and adjusted for demographics and comorbidities. The Kaplan Meier method, along with Cox proportional hazard modeling will be used for this analysis.

Additional exploratory analyses will include [redacted]

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7.4 Data Management/Audit

PRO data will be collected and managed via Moovcare®'s web-based administration systems. Demographics, quality of life, and satisfaction survey

data will be entered into the REDCap database via web-based administration. Abstracted medical record data also will be entered into a REDCap study-specific database. Moovcare® employs a secure database that is password protected. The REDCap system is a secure, HIPAA-compliant web-based application to support distributed data collection governed by standard University, School of Medicine, and Federal information security policies and standards. The REDCap application is hosted and monitored on a secure server located within the UNC CTSA-funded NC TraCS Institute's Bioinformatics Core. Access to the REDCap database for this study will be restricted to authorized research team members as needed to perform their job functions. Research staff who access the REDCap system will use a unique user ID provided by the Bioinformatics Core. Each time research staff access REDCap, a unique username and password (login) is required, and REDCap maintains an audit trail of all activity. Data transmitted between the server and end-users are encrypted using SSL, and all databases are encrypted.

Adverse events (AEs) and serious AE collection and reporting:
Adverse events (AEs) will be defined as any untoward or unexpected events or outcomes related or possibly related to a subject's participation in the ePROs. AEs will include any breach in confidentiality or embarrassment with reporting PRO symptoms and physical functioning. Delays in management of reported symptoms or complications and readmissions related to the patient's underlying condition or operative care will not be considered an adverse event related to the study as patients will be informed that any concerning symptoms or other issue may require calling the clinic or after-hours phone number (provided via the software system) or presentation to the emergency room, consistent with standard of care.

Serious AEs are not anticipated in patients related to undergoing use of the ePRO survey system or by participating in surveys for feedback on the ePRO system given the minimal risks of the study procedures. Similarly, serious AEs are not anticipated in providers completing surveys about their experience using the Moovcare® application portal.

AEs will be elicited in the free text portion of the ePRO survey. Any AEs and serious AEs willbe reported to the UNC IRB using the IRB's web-based reporting system and per protocol.

The Principal Investigator is responsible for continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC) as required. The unattended alerts will be escalated to the research coordinator who will communicate it with the clinical team. Reports of aggregate PRO responses will be provided by the statistician monthly for review at team meetings.

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 DSMC).

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 or agreeing to verbally 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. In cases when written informed consent cannot be obtained, telephone consent will be obtained, and a copy of theconsent sent to the participant.

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 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. Moovcare® or REDCap) did not initiate/reach out to patients to administer the appropriate surveys or deliver appropriate alerts. Provider not viewing/managing the alert is not considered a deviation.

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

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10.0 APPENDICES (See Attached)

- Screen shots of Moovcare® interface
- Participant Demographics Form
- Quality of Life Surveys: EORTC QLQ-30 & EORTC QLQ LC-13
- Patient satisfaction survey
- Provider satisfaction survey