PROTOCOL

ClinicalTrials.gov Identifier: NCT03249090

Protocol Title:

Electronic patient reporting of symptoms during outpatient cancer treatment: A U.S. national randomized controlled trial (the "PRO-TECT" trial)

AFT 39

Protocol Version Date:

December 5, 2020

ALLIANCE FOUNDATION TRIALS (AFT)

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Study Resources

Data Entry is through the UNC PRO-CORE Accessible at: https://pro.unc.edu/ With questions, contact UNC coordinator at: symptom_study@unc.edu Or at below contact emails/telephone numbers for UNC
Randomization Assignment Will be given to sites following IRB Approval, prior to site initiation
Site Training and Refresher Training **Will be Conducted by UNC Team** With questions, contact UNC coordinator at: symptom_study@unc.edu Or at below contact emails/telephone numbers for UNC

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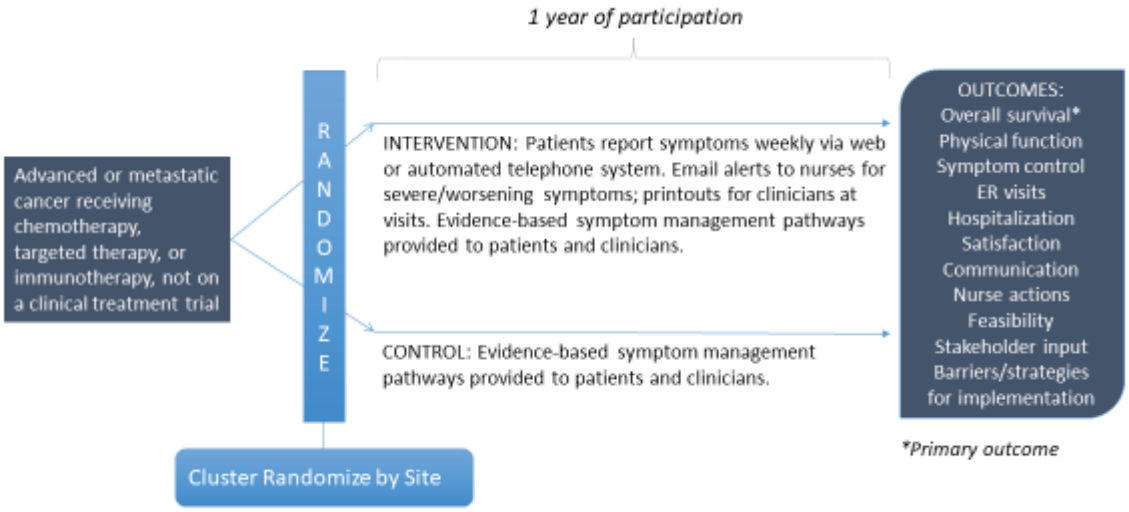
I. Synopsis and Study Schema

Study Title	Electronic patient reporting of symptoms during outpatient cancer treatment: A U.S. national randomized controlled trial
Study Acronym	PRO-TECT: Patient-Reported Outcomes to Enhance Cancer Treatment trial
Study Number	AFT-39
Study Type/Phase	RCT (not a drug trial)
Number of Study Patients	1,200 patients, from 50 (+/- 5) U.S. sites
Estimated Duration of Study	Each patient participates for up to 12 Months
Anticipated Recruitment Start Date	August 1, 2017
Rationale	Symptoms are common during cancer treatment, but frequently go undetected by clinicians between visits. Patient self-reporting of symptoms online (or automated telephone systems), with alerts to clinicians for severe symptoms, offers a potential approach to flag concerning symptoms and prevent downstream complications. A prior single-center RCT provided initial evidence of improved clinical outcomes and reduced ER visits using such an approach. The current study is designed to test nationally whether patients' outcomes and utilization of services can be improved through symptom monitoring via patient-reported outcomes between visits.
Study Objective and Outcomes	The objective is to determine whether systematic monitoring of symptoms via patient-reported outcome measures during routine cancer care delivery improves meaningful clinical outcomes. The principal (primary) outcome is overall survival. Secondary outcomes include physical functioning/ health-related quality of life/financial burden/symptom burden, emergency room/hospital utilization, duration of cancer treatment, and patient satisfaction/communication.
Qualitative and Implementation Objectives and Outcomes	Elicit perspectives about benefit-burden tradeoffs for integrating patient-reported outcomes into clinical workflow from different stakeholders, including patients, clinicians, site staff, and representatives of patient and professional organizations. Identify barriers, facilitators, and strategies used by practices to integrate patient-reported outcomes into clinical workflow. Analysis of financial impact.
Trial Design	"Cluster" RCT, randomization unit: oncology practice site (approximately 50 sites randomized in a 1:1 ratio to the "control" arm" or "intervention" arm).
Site Requirements for Participation in Trial	• Lead CRA • Clinical nursing staff champion ("Nurse Champion") for the study.
Participant Payments	• $150 gift card ($75 at baseline and $75 at 3 months) • Mailed directly to patient participants by UNC

Patient Inclusion Criteria	• Adults (21+) with metastatic cancer of any type (EXCEPT leukemia or indolent [slow growing] lymphoma) • Receiving outpatient systemic cancer treatment with palliative/non-curative intent (e.g., chemotherapy, targeted therapy, or immunotherapy) • Patients can be enrolled at any point in their cancer treatment trajectory (i.e., not just at initiation of first-line treatment) • Understands English, Spanish, or Mandarin Chinese
Patient Exclusion Criteria	• Cognitive deficits that would preclude understanding of consent form and/or study questionnaires • Current participation in a therapeutic clinical trial • Patients being treated with curative intent (e.g., adjuvant chemotherapy for breast, lung, or ovarian cancer; primary curative therapy for testis cancer or lymphoma) • Receiving hormonal therapy only (e.g., tamoxifen or aromatase inhibitors in breast cancer; androgen deprivation therapy in prostate cancer; or octreotide in neuroendocrine cancers; ibrance/palbociclib) • Indolent/slow-growing lymphoma (due to their prolonged time courses that may be minimally symptomatic) • Leukemia of any type • Does not understand English, Spanish, or Mandarin Chinese

Study Procedures	PROCEDURES AT ALL SITES (CONTROL SITES *AND* INTERVENTION SITES): • Site staff (CRA and Nurse Champion required) will attend the site initiation webinar with UNC staff, including training for the PRO-Core online data management system and orientation to the symptom management guidelines. • At enrollment, all participants will be given a booklet with patient-level symptom advice and a link to the content online. • All participants will receive $150 for participation ($75 at baseline and $75 at 3-months), mailed to them as gift cards by UNC. • CRAs will train all participants how to complete outcomes questionnaires for the trial using the PRO-Core online system. Participants will be given a choice to complete these in clinic or from home online, or if necessary via paper in clinic (with the CRA entering the data into PRO-Core). If the patient does not self-complete this information, the CRA will contact them to collect the information and then enter it into PRO-Core. The outcomes questionnaires will be completed at baseline; and at month 1 (+/- 2 weeks); and at months 3, 6, 9, and 12/off-study (+/- 4 weeks each), and will be available in English, Spanish, or Mandarin Chinese. At each time point, the CRA will contact the participant to remind them about the upcoming questionnaire and offer help. • Chart abstraction will be conducted by CRAs at baseline and at off-study for each participant, with data entered into the PRO-Core system. Date of death information will additionally be abstracted at 18 and 24 months, and possibly later per the UNC study team. • CRAs will be asked to complete a feedback survey (entered by the CRA into the PRO-Core online system) and may be asked to participate in a brief telephone debriefing and/or site visit. • Accrual will be monitored in a weekly teleconference between the UNC team and site CRAs. • At completion of the study, sites may be offered the PRO Core system for broad implementation at their site. ADDITIONAL PROCEDURES AT INTERVENTION SITES ONLY: • At baseline, CRAs will also train patients to self-report symptoms, financial burden, and physical functioning using the PRO-Core system weekly for up to a year, with a choice to do this online or via an automated telephone system (patient choice), and a choice of English, Spanish, or Mandarin Chinese. • Whenever a concerning issue is reported, an automated “email alert” notification will be sent to the site CRA. The CRA will forward the email alert to the responsible clinical nurse (or other covering clinician) and CC the site’s Nurse Champion. Within 72 hours, the CRA will document what action(s), if any, were taken by the nurse in response to the alert (entered by the CRA into a form in the PRO-Core system). • A PRO report will be printed/generated by the site CRA whenever the patient has a clinic visit and will be given to the oncologist and nurse caring for the patient.

PRO-TECT SCHEMA



II. Table of Contents

1. Background Information

1.1. Overview and Rationale

Symptoms are common among patients receiving treatment for advanced cancers and are a major cause of distress, functional disability, and emergency room/hospital utilization[1,2,3] but go undetected and unaddressed by clinicians up to half the time.[4,5,6,7] There is substantial and growing national interest to integrate electronic patient-reported outcomes (PROs) into routine practice to improve detection and management of symptoms.[8,9,10] However, the value of integrating PRO collection into routine care, acceptability to patients and clinicians, and the required infrastructure and resource needs are uncertain.[11,12,13]

Multiple studies, largely at single centers, have reported associations between routine collection of electronic PROs (e.g. symptoms reported by patients using tablets or automated telephone systems, either between visits or at visits) with improved efficiency of symptom assessment, patient-clinician communication, and satisfaction as well as symptom control, well-being, reduced emergency room utilization, longer duration of chemotherapy treatment, and improved survival.[14,15,16,17,18,19,20,21] Although this body of work suggests benefits, it is not yet definitive because a large, rigorous, multi- center controlled trial has not been conducted.

Therefore, this national multicenter cluster-randomized trial is being conducted to determine whether systematic monitoring of symptoms via PROs during routine cancer care delivery improves meaningful clinical outcomes: the "Patient-Reported Outcomes to Enhance Cancer Treatment" trial ("PRO-TECT"). The design of this trial is based on a prior large single center RCT (N=766) showing significant clinical benefits of a similar approach.[14]

1.2. Brief Description of Study Design and Intervention

This is an RCT in up to 50 (+/- 5) sites where randomization will occur in a 1:1 ratio at the site level (not at the individual patient level). Therefore, approximately 25 sites will be randomized to the PRO-TECT intervention arm (patient-reporting of symptoms plus access to a standardized symptom management guideline), and approximately 25 sites will be randomized to the control arm (usual care delivery plus access to a standardized symptom management guideline). Specifically:

PROCEDURES AT ALL SITES (CONTROL SITES *AND* INTERVENTION SITES):

- Site staff (CRA and Nurse Champion required) will attend the site initiation webinar with UNC staff, including training for the PRO-Core online data management system and orientation to the symptom management guidelines.
- At enrollment, all participants will be given a booklet with patient-level symptom advice and a link to the content online.
- All participants will receive $150 for participation ($75 at baseline and $75 at 3-months), mailed to them as gift cards by UNC.
- CRAs will train all participants how to complete outcomes questionnaires for the trial using the PRO-Core online system. Participants will be given a choice to complete these in clinic or from home online, or if necessary via paper in clinic (with the CRA entering the data into PRO-Core). If the patient does not self-complete this information, the CRA will contact them to collect the information and then enter it into PRO-Core. The outcomes questionnaires will be completed at baseline; and at month 1 (+/- 2 weeks); and at months 3, 6, 9, and 12/off-study (+/- 4 weeks

each), and will be available in English, Spanish, or Mandarin Chinese. At each time point, the CRA will contact the participant to remind them about the upcoming questionnaire and offer help.

- Chart abstraction will be conducted by CRAs at baseline and at off-study for each participant, with data entered into the PRO-Core system. Date of death information will additionally be abstracted at 18 and 24 months, and possibly later per the UNC study team.
- CRAs will be asked to complete a feedback survey (entered by the CRA into the PRO-Core online system) and may be asked to participate in a brief telephone debriefing and/or site visit.
- Accrual will be monitored in a weekly teleconference between the UNC team and site CRAs.
- At completion of the study, sites may be offered the PRO Core system for broad implementation at their site.

ADDITIONAL PROCEDURES AT INTERVENTION SITES ONLY:

- At baseline, CRAs will also train patients to self-report symptoms, financial burden, and physical functioning using the PRO-Core system weekly for up to a year, with a choice to do this online or via an automated telephone system (patient choice), and a choice of English, Spanish, or Mandarin Chinese.
- Whenever a concerning issue is reported, an automated "email alert" notification will be sent to the site CRA. The CRA will forward the email alert to the responsible clinical nurse (or other covering clinician) and CC the site's Nurse Champion. Within 72 hours, the CRA will document what action(s), if any, were taken by the nurse in response to the alert (entered by the CRA into a form in the PRO-Core system).
- A PRO report will be printed/generated by the site CRA whenever the patient has a clinic visit, and will be given to the oncologist and nurse caring for the patient.
- At completion of the study, sites may be offered the PRO Core system for broad implementation at their site.

1.3. Study Objective and Outcomes

The objective of this study is to determine whether systematic monitoring of symptoms via patient-reported outcomes (PROs) during routine cancer care delivery improves meaningful clinical outcomes, including survival, quality of life, symptom control, emergency room visits, duration of chemotherapy administration, and patient satisfaction with care. The principal (primary) outcome for the analysis is overall survival. The secondary outcomes include physical functioning/health-related quality of life/symptom burden, emergency room/hospital utilization, duration of cancer treatment, and patient satisfaction/communication.

1.4. Qualitative and Implementation Objectives and Outcomes

Additional outcomes of this study are to:

- Elicit perspectives from patients, CRAs, and clinicians about effort, benefits, and burden of patient self-reporting of symptoms with alerts and reports to clinicians.
- Identify barriers, facilitators, and strategies used by practices to integrate PROs into clinical workflow through interviews, questionnaires, and selected site visits, including impact of patient characteristics such as race, ethnicity, computer experience, or educational background.
- Obtain perspectives of stakeholders about PROs through debriefings at study completion.
- Evaluate financial impact of patient self-reporting.

2. Patient Selection and Population

2.1. Inclusion and Exclusion Eligibility Criteria

Inclusion Criteria:

1. Adults (21+) with metastatic cancer of any type (EXCEPT leukemia or indolent [slow growing] lymphoma)
2. Receiving outpatient systemic cancer treatment for non-curative/palliative intent, including chemotherapy, targeted therapy, or immunotherapy.
3. Enrolled at any point in their treatment trajectory, meaning during any line of treatment, and at any point during a course or cycle of treatment.
4. Can understand English, Spanish, and/or Mandarin Chinese.

Exclusion Criteria:

1. Cognitive deficits that would preclude understanding of consent form and/or questionnaires.
2. Current participation in a therapeutic clinical trial (because these often involve PRO questionnaires and intensive monitoring).
3. Patients being treated with *curative* intent (e.g., adjuvant chemotherapy for breast, lung, or ovarian cancer; primary curative therapy for testis cancer or lymphoma).
4. Receiving hormonal therapy only (e.g., tamoxifen or aromatase inhibitors in breast cancer; androgen deprivation therapy in prostate cancer; or octreotide in neuroendocrine cancers; ibrance/palbociclib)
5. Indolent lymphomas (due to their prolonged time courses that may be minimally symptomatic).
6. Leukemias (time courses inconsistent with other tumor types in chronic and acute leukemias).
7. Does not understand English, Spanish, or Mandarin Chinese.

3. Site Enrollment and Responsibilities

3.1. Study Site Arm Assignment and Registration (Form C1)

Patients will be enrolled from up to 50 oncology clinical practice sites across the U.S. Sites (+/- 5 sites) will be contracted by AFT and adhere to the AFT central IRB and procedures for registration and data management (including outcomes data capture in the PRO-Core clinical trial software system, which will be used for participant registration and all study forms for this trial).

The unit of randomization for this trial is the oncology practice site. Each site will be assigned as either a "Control Arm Site" or as an "Intervention Arm Site". Arm assignments will be provided to sites by the UNC study coordinating team by email to the lead CRA following site's local IRB approval and before the site's initiation/startup training webinar with UNC.

CRAs will complete the with the UNC Coordinator "Site Registration Characteristics Form" (Form C1) prior to the site initiation/startup training webinar with UNC.

3.2. Site Enrollment Required Documentation

Each site must submit the below required essential documents to the Alliance through the AFT electronic Trial Master File, accessible via the AFT website, https://alliancefoundationtrials.org/

- IRB Documents/ Approvals (Protocol, Informed Consent Form (ICF), Participant Materials, etc.)
- Institutional Informed Consent Form (a 'model' consent form will be provided to sites)
- Investigator FDA Form 1572
- Curriculum Vitae (CV) from site Principal Investigator

- Documentation of ICH Good Clinical Practice (ICH/GCP) training from site Principal Investigator
- Site CRA and site Nurse Champion study training certificates (provided by UNC after the site initiation webinar)

3.3. Site Role Requirements

3.3.1 Clinical Research Associate (CRA)

Each site will allocate effort from at least one Clinical Research Associate (CRA) to oversee processes for this trial.

CRAs at ALL SITES will:

- Oversee regulatory and logistical processes for the trial at their site
- Complete the "Site Registration Characteristics Form" (Form C1) prior to the site initiation/startup training webinar with UNC
- Participate in the site initiation/startup training webinar with UNC (and provide a training certificate from this webinar to AFT)
- Screen for eligible patients
- Oversee informed consent
- Submit clinical data at baseline and off-study for participants, and abstract date of death information at 18 and 24 months, and possibly later, per the UNC study team
- Ensure completion of outcomes questionnaires by participants or their caregivers at baseline, month 1, 3, 6, 9, and 12/off-study
- Participate in teleconferences and individual telephone calls with the central data management team as needed to discuss accrual, retention, and compliance with forms.

CRAs at INTERVENTION SITES ONLY will additionally:

- Participate in training for PRO ("patient-reported outcome") weekly survey system
- Teach patients to use the PRO system
- Forward PRO system email alerts to nurses/clinicians
- Print PRO reports for clinicians at patient visits
- Follow up with nurses after alerts (within 72 hours) and enter information about their responses to alerts in a study form
- Complete the "CRA Perspectives Survey" form after at least 6 months of site participation
- Facilitate nurse completion of the "Nurse Perspectives Survey" and "Physician Response Survey" forms after at least 6 months of site participation
- Participate in brief telephone or in-person debriefings with the study team to discuss PRO interventions and workflow.
- Contact patients after 48 hours of initial survey email/text/call to remind them to complete surveys. This will be done in coordination with the UNC Coordinator. (CRAs will be asked to avoid contacting patients more than three times each week)

3.3.2 Site Nurse Champion

Each practice site *must* designate a Nurse Champion prior to site initiation/startup training.

Nurse Champions at ALL SITES will:

- Participate in the site initiation/startup training webinar with UNC (the CRA will submit a training certificate for the nurse from this webinar to AFT)
- Facilitate dissemination of the standardized symptom management pathways to site nurses who care for study participants

Nurse Champions at INTERVENTION SITES ONLY will additionally:

- Work with UNC to figure out the optimal way to integrate PROs into the practice
- Be a resource for other clinicians and participants
- Receive a copy of email alerts being sent to clinical nurses from the CRA at that site, as an added Quality Assurance (QA) step
- Complete, or designate a participating clinical nurse with patient(s) in the study to complete, the "Nurse Perspectives Survey" form after at least 6 months of site participation; may also participate in brief telephone or in-person debriefings to discuss PRO interventions.

3.4. Data Management Software ("PRO-Core")

All data entry for this study will be conducted through the online PRO-Core data management system (https://pro.unc.edu). This includes all forms that are completed by site CRAs, and patient questionnaires. As described in the following sections, CRAs and other site staff, including the designated Nurse Champion, will be trained to use the PRO-Core system during the site initiation/startup webinar. For intervention sites only, during this webinar, site staff will also be trained how to teach patients to use the PRO weekly symptom survey system.

3.5. Site Initiation/Startup Webinar with PRO-Core Software Training

Each site will undergo a required startup meeting webinar set up by the UNC Coordinator/team, attended by the site PI, CRA(s), and designated Nurse Champion at a minimum, but optimally including all clinical nurses who might be clinically responsible for patient participants. Following training, the UNC Coordinator (not the site CRA) will complete the "Site Training Form" (Form UNC-1). Training will include instructions for using the PRO-Core software for patient registration and completion of forms. The UNC Coordinator will provide training certificates for the CRA to provide to AFT, once both the CRA and Nurse Champion are trained. Refresher trainings and trainings for new site personnel will be available at any time during the trial through the UNC coordinating center.

FOR SITES ASSIGNED TO INTERVENTION ARM ONLY:

- The CRA(s) and Nurse Champion will also be trained to use the PRO ("patient-reported outcome") weekly survey software, which is integrated with the PRO-Core data management software being used for this study. This training takes approximately 30 minutes. CRAs will be trained how to:
  - Register a patient into the PRO software
  - Select the patient's preferred mode of completing the Weekly Survey (online or automated telephone)
  - Designate the clinical nurse(s) and oncologist responsible for the care of that patient
  - Teach patients to use the PRO system from home (online or automated telephone) (typically less than 10 minutes to train patients)
  - For patients who choose the automated telephone system, how to set/reset a PIN
- Site personnel will be familiarized with the automated email alerts that will go to the site CRA when a patient reports concerning or worsening symptoms. The automated emails must be forwarded by the CRA to the appropriate clinical nurse(s) caring for the participant with a CC to the site's Nurse Champion.
- CRAs will be oriented to the wallet-sized quick-reference information cards for patient participants including instructions how to use the PRO system. These will be provided to CRAs by the UNC coordinating center.

4. Patient Recruitment and Enrollment

4.1. Identify/Select/Recruit Participants

Site CRAs will work with clinical nurses and oncologists at their practice sites to identify eligible patients. To identify potentially eligible patients, CRAs 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 waiver of authorization from the IRB. Potential patient participants may be approached and invited to be in the study by site CRAs or designated clinical staff. All eligible patients should be approached consecutively, except when "purposeful enrollment" for specific target populations is directed for sites by the UNC study team, as described below. Patients who agree to participate will review and sign the Informed Consent Form after the study is explained.

4.2. Documentation of Refusals/Ineligibility (Form C2)

Patient refusals or ineligibility to participate and reasons for refusal will be entered into the "Patient Refusal to Participate/Ineligibility Form" (Form C2).

4.3. Purposeful Enrollment

We will use purposeful enrollment to enrich the sample for historically underserved populations. This will be managed through central monitoring of accrual by UNC, with close communication with site CRAs. Enrollment methods may include restricting enrollment to specific populations after sites reach a certain number of participants (e.g. 50 or 20), and/or recruiting sites with varying patient demographics, and/or training sites to approach potential patients regardless of race, ethnicity, age, education level, or any other patient level characteristics.

4.4. Participant Registration and Study ID (Form C3)

Prior to registering the patient, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- The patient has signed an appropriate consent form and HIPAA authorization form (if applicable at your site)
- The patient has been informed about the $150 in gift cards ($75 at baseline and $75 at 3 months) that will be sent to them by UNC for participating

After written informed consent has been obtained, the study site CRA will register the patient in the PRO-Core software system by completing the "Patient Registration Form" (Form C3). In this form, the CRA will assign a unique Study ID for the patient using the three-digit code assigned to their site for the study, followed by a hyphen then a three-digit consecutive number for that patient. For example, the fifth patient registered as a participant at site #123 would be 123-005. In addition, in this form the CRA will specify, on behalf of the patient, how the patient prefers to complete questionnaires for the study: online or by an automated telephone system.

Patients enrolled but who do not participate for any reason will be considered as a Screening Failure and will not be considered as enrollees.

4.5. Baseline CRA Forms (Forms C4, C5, C7)

Each time a new participant is enrolled, the CRA will compete the baseline forms in the PRO-Core system, including: "Patient Eligibility Checklist" (Form C4), "Additional Contact Information Form" (Form C5), and "Patient Baseline Chart Abstraction Form" (Form C7). For Forms C4 and C5, consultation with the participant and/or caregiver may be necessary. Form C7 includes detailed question about the

patient's health and treatment which may require consultation with a site nurse or physician in addition to reviewing the participant's medical record. CRAs must complete the Chart Abstraction within 1 week of patient enrollment.

5. Study Procedures

5.1. Participant Training and Use of the PRO-Core System

PROCEDURES AT ALL SITES (CONTROL SITES *AND* INTERVENTION SITES):

- At baseline, all participants will be trained by the CRA how to use the PRO-Core online system to complete outcomes questionnaires for the trial.
- The outcomes questionnaires will be completed by all participants at baseline; and at month 1 (+/- 2 weeks); and at months 3, 6, 9, and 12/off-study (+/- 4 weeks each). The questionnaires are described in Table 1 and Table 2 (below).
- When more than one questionnaire is due at a given time point, they will be bundled together automatically by the PRO-Core system so that they feel like a single longer questionnaire to participants.
- Participants will be given a choice to complete these in clinic or from home online, or if necessary via paper in clinic (with the CRA entering the data into PRO-Core).
- Participants will be given a choice to complete these in English, Spanish, or Mandarin Chinese.
- Participants should be informed that their caregivers (family, friends) may assist them in any way the participant likes. The CRA may provide technical assistance. If the participant cannot complete a questionnaire, we may ask their designated caregiver(s) to complete it on their behalf. If the participant/caregiver does not complete a questionnaire on time, the CRA will contact them to collect the information (and then enter it into PRO-Core).
- The baseline questionnaire will ideally be completed in clinic with technical assistance from the CRA before the patient leaves.
- At each subsequent questionnaire time point, the CRA will contact the participant to remind them about the upcoming questionnaire, to emphasize the importance of completing the questionnaire, and to offer help.
- At completion of the study, sites may be offered the PRO Core system for broad implementation at their site.

ADDITIONAL PROCEDURES AT INTERVENTION SITES *ONLY*:

- At baseline, participants will also be trained by the CRA to self-report symptoms, financial burden, and physical functioning using the PRO (patient-reported outcome") survey system, weekly for up to a year.
- The participant will be given a choice to do this online or via an automated telephone system, and a choice of preferred type of weekly reminders to self-report (email, text message, or automated call). *This information should be specified by the CRA in Form C3.*
- For participants who select the automated telephone system, they should be assisted selecting a PIN.
- The participant should be provided with the Wallet Information Card, with information to access the system and log in (blank wallet cards can be provided to the site CRA by mail or email by the UNC coordinating center).
- The participant should be informed that if they do not complete a scheduled questionnaire, they and/or their designated caregiver(s) will receive a call from the study team.
- The participant should be informed that any time a severe or worsening symptom is reported, their nurse will be alerted. The alert will only be received during business hours, so if there is a severe symptom warranting attention off hours they should also contact the office directly. The patient should also be told that a printout of their full symptom report (i.e., PRO report) will be provided to their nurse and doctor at scheduled clinic visits.
- 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 under usual circumstances.
- At completion of the study, sites may be offered the PRO Core system for broad implementation at their site.

5.2. Provision of Symptom Advice Booklets to Participants

At baseline, the CRA will provide all participants with a symptom advice booklet, including a link to the booklet online.

These are based on best available evidence, existing guidelines, and expert consensus and are developed by CareVive, and will be supplied to CRAs by UNC.

5.3. Provision of Symptom Management Pathways to Nurses

Nurses involved with the clinical care of participants in this study will be provided with access to evidence-based symptom management pathways from CareVive on paper and/or electronically. The Nurse Champion and ideally the clinical nurses at all participating sites (intervention and control arm sites) will be provided with the pathways at the time of startup/training for this study. Whenever a new patient is enrolled to the study, the pathways should be sent to a clinical nurse responsible for their care.

5.4. Participant Weekly PRO Surveys - INTERVENTION SITES ONLY

As described above, all participants in the intervention arm will be asked to complete weekly PRO ("patient-reported outcome") surveys from home each week via the PRO-Core system describing their symptoms, financial burden, and physical functioning. They will receive baseline training by the CRA with a choice to complete the surveys online or an automated telephone system, with automated reminders by email, text, or an automated call.

5.4.1 Automated Reminders for PRO Surveys - INTERVENTION SITES ONLY

Each week, patient participants at intervention sites will receive an email/text (for online) or automated call (for the phone system) as a reminder to self-report. At the time of registration, patients will be able to select their preferred day and time to receive their email/text/call each week. They will be able to change this if desired at anytime throughout the study.

The email/text will contain a link to the PRO questions, and the call will allow the participant to answer and respond to the questions using the numbers on their phone (either a land line or a cell phone will work). If a patient participant does not complete a weekly PRO survey after the initial email/text/call reminder, they will receive one additional automated reminder over the next 24 hours (during daytime hours).

5.4.2 CRA Backup Calls for Missed PRO Surveys - INTERVENTION SITES ONLY (Form C6)

If, after 48 hours, they have not completed the survey their CRA/UNC contacts them (e.g. by phone, in person, or email). The CRA/UNC Coordinator will administer the questions verbatim and enter them into PRO Core (marking that they were interview administered.). Reasons for the patient not completing the study questionnaire on their own should be entered into the C8 Patient Contact Log. If the patient does not complete the weekly study questionnaire, the CRA/UNC Coordinator will complete the C6 Missing Data Form to ascertain the reason for the missed questionnaire. This information should be collected as soon as possible, and can be collected up until the day before the next scheduled PRO weekly survey. We are asking that the patient not be contacted more than three times by the CRA/UNC each week (if possible). This backup strategy improves data completeness.

5.4.3 Automated Alerts - INTERVENTION SITES ONLY

Each time a patient self-reports an issue of a concerning level or that increases from the prior self- report, an automatic email alert notification will be triggered to the site CRA. The alert will only include the participant's study ID, not their identifying information. The CRA will be responsible for adding the patient's name, medical record number, and contact information to the email, then forwarding the email to the appropriate site clinical nurse caring for the patient immediately upon receipt, with a CC to the Nurse Champion. These alert notifications will include a link to evidence-based symptom management pathway recommendations when applicable that can be quickly and easily referenced by the nurse.

5.4.4 CRA Follow Up of Nurse Actions Taken in Response to Alerts - INTERVENTION SITES ONLY (Form C11)

Within 72 hours of each alert, the CRA should contact the nurse to ascertain what action(s) was taken in response to the alert using the" Nursing Alert Response Form" (Form C11). This form offers several options that should be asked or printed

or pasted into an email and given to the nurse as choices (below), and the nurse's response should be used by the CRA to complete Form C11.

Was the patient contacted?

( ) Yes
( ) No

How was the patient contacted (select all that apply)?

[ ] In person
[ ] By phone or text
[ ] By email
[ ] By patient portal

If by phone, did you leave a voicemail?

( ) Yes
( ) No

Select any discussion that occurred (select all that apply):

[ ] Discussed symptom with patient
[ ] Discussed symptom with caregiver
[ ] Discussed with other clinician(s)

Select any action/advice that occurred (select all that apply):

[ ] Supportive medication – prescribed or modified dose/schedule (e.g., anti-emetic)
[ ] Patient will use over-the-counter (OTC) medication at home (e.g., analgesic, Senna)
[ ] Chemotherapy - dose changed or held
[ ] Sent to emergency room/urgent care/admitted to hospital
[ ] Imaging or laboratory test ordered
[ ] Appointment made to come in to clinic for evaluation
[ ] Referral made to another clinic
[ ] Patient will use self-management strategies at home (e.g., meditation, walking)

Select reason if no action/advice occurred (select all that apply):

[ ] Already aware of symptom, so no action taken
[ ] Symptom resolved itself
[ ] Symptom unrelated to chemo (e.g., cold symptoms)
[ ] Will discuss with patient during next visit

Brief description (you can describe any detail or reason that action was taken or not taken):

5.4.5 Printed PRO Reports for Clinicians at Visits - INTERVENTION SITES ONLY

At each scheduled clinic visit for a participant, the site CRA will provide a Printed PRO Report for the participant to the nurse and oncologist seeing the participant, generated by the PRO-Core software system.

5.5. Outcomes Assessments and Timeline

This trial includes questionnaires for patients and forms for CRAs and nurses to complete. All of these are found in the PRO-Core software system. **Table 1 and Table 2**, at the bottom of this section, outline the various questionnaires/forms and time points for completion. There is a window of time for completion of most forms. Form completion is monitored centrally by UNC, and assistance with form completion and data collection may be offered by or requested from UNC personnel.

5.5.1 Outcomes Questionnaires for Participants (Questionnaires P1, P2, P3, P4)

As noted above, the participant questionnaires for assessing outcomes (P1, P2, P3, P4) in this trial may be bundled together automatically when administered electronically by the PRO-Core system, so that they feel like a continuous longer questionnaire, rather than individual questionnaires. They are available in English, Spanish, or Mandarin Chinese. The outcomes questionnaires will be completed at baseline; and at month 1 (+/- 2 weeks); and at months 3, 6, 9, and 12/off-study (+/- 4 weeks each), and will be available in English, Spanish, or Mandarin Chinese. Participants will be given a choice to complete these in clinic or from home online, or if necessary via paper in clinic (with the CRA entering the data into PRO-Core).

If a patient questionnaire is completed on paper, the site CRA must scan (or mail) the paper questionnaire to the UNC Coordinator. The UNC coordinator will complete a QA check, comparing the hard copy to what was entered into PRO-Core. If discrepancies are found, the UNC Coordinator will review them with the CRA and correct any errors in PRO-Core.

If the patient does not self-complete this information, the CRA will call them to collect the information and then enter it into PRO-Core. At each questionnaire time point, the CRA will contact the participant to remind them about the upcoming questionnaire, and to offer help.

If the patient goes off study prior to week 52 the CRA must contact the patient as soon as possible to get the off-study surveys completed.

Note for intervention sites only: The outcomes questionnaires are different from the Weekly Symptom Surveys that patients at intervention sites will be asked to complete. Therefore, participants at intervention sites will be asked to complete both the Weekly Symptom Surveys, and the periodic outcomes questionnaires. These will be completed separately from each other, although all of these are completed using the PRO-Core software.

The patient outcomes questionnaires include:

- **Patient Demographics Questionnaire (Questionnaire P1) – ALL SITES:** This questionnaire asks participants about their baseline information and will be administered at the time of enrollment.
- **Patient Quality of Life Questionnaire (Questionnaire P2) – ALL SITES:** The outcomes of physical functioning, health-related quality of life, and symptom control will be assessed by items from the "EORTC-QLQ-C30", which will be administered to each patient participant in the "Patient Quality of Life Questionnaire" (Form P2) at baseline; at month 1 (+/- 2 weeks); at months 3, 6, 9; and at month 12/off-study (+/- 4 weeks each). The EORTC QLQ-C30 is a well-established and frequently used questionnaire[22,23,24] that includes a 5-item physical functioning domain, individual symptom items corresponding to the symptoms in the PRO intervention system, and a composite quality of life score.[22,23,24] The QLQ-C30 has been rigorously tested for its psychometric properties in qualitative and quantitative studies and has been widely used in clinical studies in oncology, and is a standard measure used across oncology drug development trials and in many ALLIANCE national clinical trials.
- **Patient Satisfaction Questionnaire (Questionnaire P3) – ALL SITES:** This questionnaire will be administered to each participant at baseline and 3 months of participation (+/- 4 weeks for the month 3 form). 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,[25] and from the "Patient-Centered Communication in Cancer Care" short form questionnaire (PCC-CA-6).[26] Participants or their designated caregivers may also be contacted by UNC for follow up questions about their responses.
- **Patient PRO Feedback Questionnaire (Questionnaire P4) – INTERVENTION SITES ONLY:** In the intervention arm only, this questionnaire will be administered to patients after 3 months of participation (+/- 4 weeks). This questionnaire includes items about the ease and perceived value of using the PRO system. This information will be useful for dissemination and future implementation efforts. Understanding these perspectives is essential to avoid unnecessary burden and to optimize convenience and benefits.

5.5.2 Date of Death Form (Form C9)

The CRA will abstract the medical chart and/or touch base with the clinical team caring for participants to assess if the

patient has died, the date of death, and whether COVID may have played a role. Form C9 should be completed at off-study for each participant, as well as 18 months and 24 months following the date of enrollment for that patient. Subsequent chart abstraction/information about date of death may be requested if needed for the outcomes assessment by the UNC study team. Dates of death for participants will be verified or sought by the UNC study team linking participant information to national governmental databases (e.g., the CDC National Death Index).

5.5.3 CRA and Nurse Perspectives Surveys - Intervention Sites Only (Forms C10 & N1)

The amount of staff effort for PRO-related activities will be assessed based on data completed by CRAs in the "CRA Perspectives Survey" (Form C10) and by nurses in the "Nurse Perspectives Survey" (Form N1), which will be completed at least six months from the time the initial participant at their site is enrolled. The nurse survey will also assess perceived value and use of patient-reported outcomes (PROs) in practice, impressions of barriers to implementation of PROs in practice and facilitators. In addition, to supplement these surveys, telephone or on-site debriefings with staff and clinicians will be conducted to understand perceptions of PRO integration into clinical practice and workflow. These data will be informative towards future implementation efforts. The UNC Coordinator may contact the CRA and nurse to remind them to complete perspectives surveys at six months.

5.5.4 Off Study Chart Abstraction Form (Form C12)

A detailed form (Form C12) requiring information to be abstracted from the participant's medical record must be completed by the CRA when the participant goes off study (+ 4 week window for form completion). Consultation with a site nurse or physician may be necessary for clarifications of some of the questions in this form. For example, this form includes information about 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. Additional outcomes data may be elicited by the UNC team by linking patient records to administrative databases. The UNC Study Team may request clarifications or substantiation of outcomes data from sites, and may elect to audit sites for verification of data.

5.5.5 Physician Response Form (Form Onc1)

Physician impressions and usage of the Patient PRO Report will be assessed based on data provided by oncologists in the "Physician Reponses Survey" (Form Onc 1). The CRA will ask one treating oncologist who had experience using the report to complete this brief survey after the study has been open at the site for at least 6 months. These data will be informative towards future implementation efforts. The UNC Coordinator may contact the CRA to remind them to ask the treating oncologist to complete the survey.

6. Timeline for Study Forms and Questionnaires

- **Table 1**, below, shows the schedule of study assessments by patients, CRAs, and clinicians (nurses/oncologists) for **CONTROL** sites only.
- **Table 2**, below, shows the schedule of study assessments by patients, CRAs, and clinicians (nurses/oncologists) for **INTERVENTION** sites only.

Table 1. Timeline for Control Sites Only

Source	Measure	Contents/Notes	Month of Patient Participation												Post	
			Base-line	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12 (or Off Study)*	*18*	24
Patient Reported (English, Spanish, Mandarin Chinese)	**P1. Patient Demographics**	Baseline characteristics	X														
	P2. Patient Quality of Life Questionnaire*	EORTC QLQ-C30 questions	X	X		X			X			X			X		
	P3. Patient Satisfaction Questionnaire*	CAHPS questions	X			X									X		
CRA Reported	**C1. Site Registration & Characteristics**	Site characteristics	Completed by CRA after a site has contracted to participate in the trial														
	C2. Patient Refusal to Participate/Ineligibility	Reason(s) and basic patient data	X														
	C3. Patient Registration	CRA must create/enter a unique patient ID; Some info requires abstracting medical record and input from patient or clinicians	X														
	C4. Patient Eligibility Checklist		X														
	C5. Additional Contact Information Form		X														
	C7. Patient Baseline Chart Abstraction Form	Info abstracted by CRA from participant's medical record	X														
	C9. Date of Death Form														X	X	X
	C12. Off Study Chart Abstraction Form**														X		
UNC	**UNC1. Site Training**	Details of startup meeting	X														

** **The 3-month data collection is the key time point and is the most important date to have complete data collection**. The patient questionnaires may be "bundled" together automatically by the PRO-Core software so it feels like a single longer questionnaire to participants. For Form P2, the timeframe is +/- 2 weeks for the month 1 form, and +/- 4 weeks for the months 3, 6, 9, and 12 forms. For Form P3 and Form P4, the timeframe for the month 3 and month 12 forms is +/- 4 weeks. If a participant does not complete a form within the specified time frame, the site CRA or UNC Coordinator should contact the patient to obtain this information. The site CRA and UNC Coordinator will work it out between them who will contact the patient.*
*** Window for completion is + 4 weeks.*

Table 2. Timeline for Intervention Sites Only

Source	Measure	Contents/Notes	Month of Patient Participation													Post	
			Base-line	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12 (or Off Study)*	*18*	*24*
Patient Reported (English, Spanish, Mandarin Chinese)	**Weekly PRO Survey – *Intervention Sites Only***	Symptom questions reported from home	X	X	X	X	X	X	X	X	X	X	X	X	X		
	P1. Patient Demographics	Baseline characteristics	X														
	P2. Patient Quality of Life Questionnaire*	EORTC QLQ-C30 questions	X	X		X			X			X			X		
	P3. Patient Satisfaction Questionnaire*	Questions about PRO system	X			X									X		
	P4. Patient PRO Feedback Booklet – *Intervention Sites Only**	CAHPS questions				X									X		
CRA Reported	**C1. Site Registration & Characteristics**	Site characteristics	Completed by UNC after a site has contracted to participate in the trial														
	C2. Patient Refusal to Participate/Ineligibility	Reason(s) and basic patient data	X														
	C3. Patient Registration	CRA must create/enter a unique patient ID; Some info requires abstracting medical record and input from patient or clinicians	X														
	C4. Patient Eligibility Checklist		X														
	C5. Additional Contact Information Form		X														
	C6. Missed Weekly Patient PRO Survey – *Intervention Sites Only*[§]	Info collected from patients by site CRA (or assisted by UNC)	Collected if participant misses a scheduled *Weekly PRO Survey*. Reason for missed survey should be selected.														
	C7. Patient Baseline Chart Abstraction Form	Info abstracted by CRA from medical record	X														
	C8. Patient Contact Log for Missed PRO Survey – *Intervention Sites Only*[§]	Info collected from patients by site CRA (or assisted by UNC)	Completed after successful or unsuccessful attempts to contact participants to collect information for *Form C6*.														
	C9. Date of Death Form	Info abstracted by CRA from medical record													X	X	X
	C10. CRA Perspectives– *Intervention Sites Only*[§]	Questions for CRAs about PRO system	To be completed after study has been open at site for at least 6 months.														
	C11. Nursing Alert Response Form– *Intervention Sites Only*	CRA obtains responses from clinical nurse who got the alert	Collected within 72 hours of each nursing alert notification, to elicit actions taken by clinical nurse in response to the alert														
	C12. Off Study Chart Abstraction Form**	Info abstracted by CRA from medical record													X		
	Printed PRO Report	Patients' symptoms	Printed for oncologist and nurse at clinic visits.														
Nurse Reported	**N1. Nurse Perspectives– *Intervention Sites Only*[§]**	Questions about PRO system	To be completed after study has been open a site for at least 6 months.														
Oncologist Reported	**Onc1. Physician Response Form**	Questions about PRO Report Usage	To be completed after study has been open a site for at least 6 months.														
UNC	**UNC1. Site Training**	Details of startup meeting	X														

** **The 3-month data collection is the key time point and is the most important date to have complete data collection**. The patient questionnaires may be "bundled" together automatically by the PRO-Core software so it feels like a single longer questionnaire to participants. For Form P2, the timeframe is +/- 2 weeks for the month 1 form, and +/- 4 weeks for the months 3, 6, 9, and 12 forms. For Form P3 and Form P4, the timeframe for the month 3 and month 12 forms is +/- 4 weeks. If a participant does not complete a form within the specified time frame, the site CRA or UNC Coordinator should contact the patient to obtain this information. The site CRA and UNC Coordinator will work it out between them who will contact the patient.*

*** Window for completion is + 4 weeks.*

[§] To be completed after the study has been open at a site for at least 6 months. The form should be collected within a week of this time point, but there is no expiration on the timeframe for collecting these up through study closure.

[‡] The site CRA and UNC Coordinator will work it out between them who should be contacting their site's participants who do not complete the Weekly PRO Survey on time (within 24 hours) for backup/reminder/questions. This information should be collected as soon as possible but can be collected up until the day before the next scheduled Weekly PRO Survey.

6.1. Linkages to National Databases for Outcomes Assessment

Additional information such as utilization of services or deaths may be collected from national databases to which participant records are linked. Information to link participants' records to these databases will be provided by sites or participants.

6.2. Debriefings with Participants or Caregivers

Participants or their designated caregivers may be contacted by the UNC study team to follow up on responses to outcomes questionnaires.

6.3. Monitoring Accrual and Retention of Participants

Accrual will be monitored by regular contacts between the UNC Coordinator and site CRAs. The UNC Coordinator and AFT staff will continuously be in contact with site CRAs to monitor for any concerns or difficulties.

6.4. Off-Study Timing and Procedure

Patient participants are asked to remain on the study completing questionnaires for 12 months (52 weeks), or until they go off-study prior to that time. Reasons for patients to go off-study include:

- Completion of 12 months (52 weeks) of participation
- Discontinuation of chemotherapy treatment (estimated to last greater than or equal to 3 Months)
- Initiation of hospice
- Death
- Moved to a different oncology practice for cancer care
- Voluntary disenrollment

When a patient completes their 12th month of participation or goes off-study prior to then, the "Off Study Chart Abstraction Form" (Form C12) must be completed. If the patient has died at that time, the "Date of Death Form" (Form C9) must be completed.

In addition, if a patient goes off study early for any reason other than death, they should complete the final Outcomes Questionnaires (including: "Patient Quality of Life Questionnaire" (Form P2), the "Patient Satisfaction Questionnaire" (Form P3), and *for intervention sites only* the "Patient PRO Feedback Questionnaire" (Form P4) as soon as possible.

6.5. Organizational Perspectives on Benefit-burden Tradeoffs

At the completion of the trial when preliminary results are available, semi-structured teleconferences will be held with representatives of national patient and professional organizations to elicit perspectives on whether the observed level of staff/patient effort and cost for PRO collection is 'worth it' for the observed benefits. No identifying information will be collected from the interviewees. These results will anchor the trial's results to organizational impressions of value towards dissemination and implementation.

7. Statistical Considerations

7.1. Statistical Tests

The principal (primary) outcome is overall survival. Overall survival will be compared between arms using a stratified log-rank test (stratified by cancer type, with a sandwich estimator to account for site clustering). Each patient will be analyzed according to his/her site's randomized assignment (intent-to-treat approach). In keeping with evolving scholarly thinking, we will not consider any specific threshold of statistical significance in deeming the intervention in this trial a success, and instead the outcome of the study will be based on interpretation of all conducted analyses taking into account both statistical and clinical significance (Wasserstein RL, Schirm AL, Lazar NA. The American Statistician. 2019; 73[sup1]:1-19.). Due to the potential impact of COVID on the outcomes in this trial, and potential differential impact of COVID on clusters in the two randomization arms, adjustments in analyses may be made and a sensitivity analysis will be conducted in which overall survival data are censored at March 1, 2020.

For the trial's secondary analyses, emergency room/hospital utilization and duration of cancer treatment will be compared between arms using stratified Fine-Gray competing risk regression with death as a competing event (stratified by cancer type, with robust sandwich covariance matrix estimates to account for site clustering). Physical function/health-related quality of life/symptom burden/financial burden as measured by the QLQ-C30 at 3 months and patient satisfaction/communication as measured by CAHPS items will each be compared between arms using a general linear mixed model approach including a fixed effect for cancer type, a random effect for site, and a continuous covariate for the corresponding baseline score. All other quantitative outcomes will be tabulated within arms descriptively (see below for separate description of qualitative analyses). While a focus of the non-survival assessments is the 3-month time point, analyses will include each post-baseline assessment time point (1, 6, 9, and 12 months) as well as longitudinal analyses incorporating all post-baseline PRO data. Supplemental analysis will also include multivariable analysis of each primary outcome including the following covariates: age (<60 versus ≥60), gender (female versus male), race/ethnicity (white non-Hispanic versus other), education status (high school graduate/GED or less versus some college or more), disease type (e.g., gastrointestinal, genitourinary, gynecologic, breast, lung/head and neck, melanoma, versus other), prior computer/email/internet use (rarely or less versus sometimes or more), and oncology practice site location (predominantly urban/suburban vs rural). Subgroup analyses may also be conducted for each of these covariates. For patients who die, have missing data, or go off study before the time point of analysis, prior or off study data (whichever is later) may be carried forward. Similar to above, sensitivity analyses may be carried out with truncation of data at March 1, 2020, to assess for impact of COVID.

7.2. Sample Size/Power

For overall survival with a total of 1,200 patients at 52 sites nationally, there will be at least 90% power for a hazard ratio of 0.76 (based on the prior single-center RCT) which is considered clinically meaningful[28,29] using a two-sided alpha=0.05 log-rank test with 576 observed events, computed using the formula by Xie and Waksman[30] with an intracluster correlation coefficient of 0.001 (estimated from the 10 largest legacy ALLIANCE trials involving 12,717 total patients). This power calculation further assumes drop-out of 150 patients in the first 2.5 years. Overall survival analysis will be undertaken when the number of events has been observed and data collection for secondary outcomes is sufficient. Statistical analysis will use all deaths recorded in the database at time of analysis including deaths in excess of the number needed to trigger the planned analysis.

7.3. Missing Data/Sensitivity Analyses

Missing data will be minimized through site training, human backup calls to patients for missed assessments, and automatic and human real-time central monitoring of data compliance. The impact of missing data will be investigated using sensitivity analyses.

7.4. Qualitative Data Collection and Analyses

UNC personnel will conduct interviews with intervention sites during site visits and over the phone with personnel and patients, supported by the UNC CHAI-Core. Patient interviews will be exclusively completed over the phone. Standardized interview guides will provide interviewers with a detailed script to follow, and open-ended probes will allow stakeholders the opportunity to answer questions in their own way.[31,32, 33] Potential follow-up probes to clarify answers from stakeholders will also be included. Interview scripts will be tailored based on the type of stakeholder (e.g., administrative staff, clinician, or patient). Interviews should last between 45 and 60 minutes and will be audio recorded. Interviewers will populate standardized summary sheets during the interviews. Transcripts will be produced by a professional transcription service and will be coded for analysis themes using standard qualitative software.

7.5. Randomization

Sites will be randomly assigned to each arm in a 1:1 ratio by the AFT Statistical Center based at the Mayo Clinic, using permuted block randomization with random block size of 2 or 4 stratified by rural vs. urban location. The randomization sequences (one for each stratum) will remain concealed and arm assignments will only be revealed one at a time as sites are registered by the UNC Coordinator.

8. Protection of Human Subjects

Potential risks for participants include inconvenience (clinic or home schedule interrupted), questionnaire burden (being asked to respond to a series of questions), disinterest (not finding the study involvement to be meaningful), loss of anonymity (being seen by others on the clinical team when the study team approaches to inform them of the study), or loss of confidentiality (if a study team member shared information given by the participant to others not involved in the study). Research team members at all sites will be instructed to keep all patient participation and data confidential. We do not anticipate physical, financial, or legal risks to participation. Registrations of human subjects on AFT studies require that institutions obtain informed consent prior to registration and the start of study interventions.

8.1. AFT Policies and Protections

AFT has in place policies and procedures to ensure the protection of human subjects and to safeguard the rights and welfare of human subjects. AFT requires that institutions participating in AFT research studies hold a Federal-wide Assurance (FWA) with the Office for Human Research Protections (OHRP). The AFT also ensures that IRBs are registered, and that site IRBs provide a level of IRB review that is appropriate to the type of research being conducted. The AFT staff works closely with site personnel to assist them with their questions and any corrective actions necessary to ensure the protection of human subjects. To protect against potential risks across all sites, study team members will be instructed not to disclose participation or content of participation to anyone outside of the study team.

8.2. Computer and Electronic Protection

Data collection across sites will be through the University of North Carolina (UNC) PRO-Core web-based platform for secure questionnaire administration. Data are stored in 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. The PRO-Core also has additional protections when multiple sites are involved. For instance, recruitment sites will only be able to see their own patients' information.

8.3. Confidentiality

Strict confidentiality will be maintained. Hard-copy research data will be minimal and stored in locked filing cabinets in locked offices at the enrolling site. Research data will be maintained in separate charts, identified by ID number only, and secured in locked files. A master list connecting names and ID numbers will be kept in a separate, secure location. Only authorized members of the investigative group will have access to secured files, and will be educated regarding the 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.

8.4. Protection Against Risks from Interviews

Telephone debriefings and site visits will be conducted to understand site workflows and uptake of PROs. UNC study team members will be trained in interviewing procedures in order to conduct these debriefings. The team has conducted multiple studies with in-depth interviews. Interviewers will be reminded to conduct interviews in a private office. Audio recordings of interviews will be stored as electronic files on password-protected computers. The recordings will not be labeled with personal identifiers. The information linking study ID numbers/initials with the participant's identity will be kept in a separate, secure location. Interviews will be supported by the UNC CHAI Core.

Transcription will be conducted by Landmark Associates, Inc. ("Landmark"). All Landmark employees have completed CITI training and NIH's Protecting Human Research Participants training. All of Landmark's employees, contractors, and executive staff are also under non-disclosure agreements. For maximum security, Landmark transfers data from its customers and its offsite servers via SSL encrypted endpoints. All files are uploaded and downloaded through Salesforce.com's Customer Portal. The servers that store all of Landmark's client data are managed by Amazon Web Services, a division of Amazon.com LLC. Specifically, the files are located on their Simple Storage Service (S3). The files are protected behind pre-signed URL's that are generated for each file that is uploaded to the server. The generated links are set to expire in 60 seconds. Access to the Amazon Web Services dashboard requires the admin user to have possession of a Hardware Multi-Factor Authentication (MFA) Device. A link to the AWS White Paper on Security is here: http://media.amazonwebservices.com/pdf/AWS_Security_Whitepaper.pdf Upon receiving a password-protected login, only authorized project personnel will be able to upload files to Landmark's website through the Customer Portal.

8.5. Potential Benefits and Importance of Knowledge to Be Gained

Patient-reporting of symptoms and physical function may improve quality of care by identifying symptoms before they lead to adverse outcomes such as functional impairment, hospitalization, or chemotherapy dose reduction. No harms of patient PRO reporting have been identified in prior research. Therefore, participants in these studies may benefit by burdensome symptoms being identified earlier and communicated to clinicians. Moreover,

completing symptom questionnaires may assist patients to become more aware of their symptoms, and move towards better communication and self- efficacy (as suggested in prior work).

The knowledge sought in the proposed research can have direct clinical benefits for patients with cancer enrolled in future clinical trials and/or routine cancer treatment. These gains include more accurate monitoring of symptoms and toxicities that can prompt clinician intervention. This will allow for broad collection of patients' symptoms in clinical research and practice, potentially benefitting many patients whose symptoms might otherwise go undetected. Although the risks in the proposed research are not non-existent, the current and future benefits of improved quality of care and symptom monitoring balance the risks of inconvenience, questionnaire burden, loss of anonymity, disinterest, and/or loss of confidentiality.

9. Ethical Considerations and Administrative Procedures

9.1. Regulatory and Ethical Compliance

The Investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his or her personnel and local IRB. Study documents will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study. This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines. The investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

9.2. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator including the CRA (if acceptable by local guidelines), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study). Consent forms will be available in English, Spanish, and Mandarin Chinese. It is the investigator's (or designee's) responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial- related procedure.

9.3. Responsibilities of the Investigator/IRB/IEC/REB

The Investigator is responsible for ensuring that their study team maintains and retains all study related documentation, including but not limited to: signed Informed Consent Forms, medical records that are applicable for this study and source documents, the study protocol, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic forms in the PRO-Core software system in a timely manner.

9.4. Protocol Deviations

The Investigator is responsible to document and explain any deviations from the approved protocol. The Investigator should promptly report any deviations that might impact patient safety and data integrity to the respective IRB in accordance with local IRB policies and procedures.

9.5. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including substantial changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the Investigator(s) and approved by relevant IRBs prior to implementation. Administrative changes of the protocol or small changes to study forms or questionnaires are considered minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These changes will be released by the AFT, agreed by the investigator(s), and notified to the IRB.

9.6. Retention of Records

Any records and documents relating to the conduct of this study must be retained by the Investigator until notification by UNC/AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

9.7. Data Confidentiality

Patient medical information is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. The overall results of any research study will be available in accordance with the effective AFT policy on study data publication. Patient information may be used to link to national databases to retrieve outcomes assessment information, which will be stored in de-identified databases.

9.8. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will provide accurate participant data into study forms with observations pertinent to the study.

The Clinical Research Associate (CRA) or designated study site personnel will complete the Forms in a timely manner. Subjects will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a site number, subject number. At study completion, when the database has been declared to be complete and accurate, the database will be locked.

UNC and/or AFT study personnel will review forms for completeness and accuracy; any discrepancies will be resolved with the site CRAS, investigator or designee, as appropriate. All changes to the study database will be documented.

If an Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself. The Investigator must obtain AFT's written permission before disposing of any records, even if

retention requirements have been met.

9.9. Site Audits

The UNC study team may request clarifications or substantiation of outcomes data from sites, and may elect to audit sites for verification of data. Site audits may also be conducted by representatives of AFT according to AFT policies and procedures.

9.10. Publication of Study Protocol and Results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs. No investigator may present or publish any portion of this trial without written approval from UNC and AFT.

10. References

[1] Basch, E. Toward patient-centered drug development in oncology. N Engl J Med 2013;369(5):397-400.

[2] Reilly CM, Bruner DW, Mitchell SA, Minasian LM, Basch E, Dueck AC, Cella D, Reeve BB. A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. Support Care Cancer. 2013;21(6):1525-50.

[3] Henry DH, Viswanathan HN, Elkin EP, Traina S, Wade S, Cella D. Symptoms and treatment burden associated with cancer treatment: results from a cross-sectional national survey in the U.S. Support Care Cancer. 2008;16(7):791-801.

[4] Cleeland CS, Zhao F, Chang VT, Sloan JA, O'Mara AM, Gilman PB, Weiss M, Mendoza TR, Lee JW, Fisch MJ. The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. Cancer. 2013 Dec 15;119(24):4333-40.

[5] Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. J Clin Oncol. 2004;22(17):3485-90.

[6] Eivor A Laugsand, Mirjam AG Sprangers, Kristin Bjordal, Frank Skorpen, Stein Kaasa, Pål Klepstad. Health care providers underestimate symptom intensities of cancer patients: A multicenter European study. Health Qual Life Outcomes. 2010;8:104.

[7] Atkinson TM, Li Y, Coffey CW, Sit L, Shaw M, Lavene D, Bennett AV, Fruscione M, Rogak L, Hay J, Gönen M, Schrag D, Basch E. Reliability of adverse symptom event reporting by clinicians. Qual Life Res 2012;21:1159-1164.

[8] Fung CH, Hays RD. Prospects and challenges in using patient-reported outcomes in clinical practice. Qual Life Res. 2008;17(10):1297-302.

[9] Conway PH, Mostashari F, Clancy C. The future of quality measurement for improvement and accountability. JAMA. 2013 Jun 5;309(21):2215-6.

[10] National Quality Forum. Patient-reported outcomes (PROs) in performance measurement. January 10,2013. Available at: www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx.

[11] Wu AW, Kharrazi H, Boulware LE, Snyder CF. Measure once, cut twice—adding patient-reported outcome measures to the electronic health record for comparative effectiveness research. J Clin Epidemiol. 2013 Aug;66(8 Suppl):S12-20.

[12] Howell D, Molloy S, Wilkinson K, Green E, Orchard K, Wang K, Liberty J. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. Ann Oncol. 2015 Sep;26(9):1846-58.

[13] Snyder CF, Aaronson NK, Choucair AK, Elliott TE, Greenhalgh J, Halyard MY, Hess R, Miller DM, Reeve BB, Santana M. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. Qual Life Res. 2012;21(8):1305-14.

[14] Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM, Chou JF, Dulko D, Sit L, Barz A, Novotny P, Fruscione M, Sloan JA, Schrag D. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol. 2016;34:557-565.

[15] Valderas JM, Kotzeva A, Espallargues M, Guyatt G, Ferrans CE, Halyard MY, Revicki DA, Symonds T, Parada A, Alonso J. The impact of measuring patient-reported outcomes in clinical practice: a systematic review of the literature. Qual Life Res. 2008;17(2):179-93.

[16] Chen J, Ou L, Hollis SJ. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. BMC Health Serv Res. 2013;13:211.

[17] Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, Macgillivray S. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014 May 10;32(14):1480-501.

[18] Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA. 2002;288(23):3027-34.

[19] Basch E, Artz D, Dulko D, Scher K, Sabbatini P, Hensley M, Mitra N, Speakman J, McCabe M, Schrag D. Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol. 2005;23(15):3552-61.

[20] Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, Selby PJ. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol. 2004;22(4):714-24.

[21] Berry DL, Blumenstein BA, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M, Bush N, Karras BT, Lober WB, McCorkle R. Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. J Clin Oncol. 2011;29(8):1029-35.

[22] European Organisation for Research and Treatment of Cancer (EORTC). QLQ-C30 Information. Available at: http://groups.eortc.be/qol/eortc-qlq-c30

[23] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

[24] Gundy CM, Fayers PM, Groenvold M, Petersen MA, Scott NW, Sprangers MA, Velikova G, Aaronson NK. Comparing higher order models for the EORTC QLQ-C30. Qual Life Res. 2012 Nov;21(9):1607-17.

[25] Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey system. Available at: https://cahps.ahrq.gov/about-cahps/index.html

[26] Reeve BB, Thissen DM, Bann CM, Mack N, Treiman K, Sanoff HK, Roach N, Magnus BE, He J, Wagner LK, Moultrie R, Jackson KD, Mann C, McCormack LA. Psychometric evaluation and design of patient-centered communication measures for cancer care settings. Patient Educ Couns. 2017 Feb 10. pii: S0738-3991(17)30075-7.

[27] Adams G, Gulliford MC, Ukoumunne OC, Eldridge S, Chinn S, Campbell MJ. Patterns of intra-cluster correlation from primary care research to inform study design and analysis. J Clin Epidemiol. 2004 Aug;57(8):785-94.

[28] Sobrero AF, Pastorino A, Sargent DJ, Bruzzi P. Raising the bar for antineoplastic agents: how to choose threshold values for superiority trials in advanced solid tumors. Clin Cancer Res. 2015 Mar 1;21(5):1036-43.

[29] Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, Garrett-Mayer E, Herbst RS, Lilenbaum RC, Sima C, Venook AP, Gonen M, Schilsky RL, Meropol NJ, Schnipper LE. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.

[30] Xie T, Waksman J. Design and sample size estimation in clinical trials with clustered survival times as the primary endpoint. Stat Med. 2003; 22(18):2835-46.

[31] McCracken G. The long interview. Newbury Park, CA: Sage; 2008.

[32] Krippendorff K. Content Analysis: An Introduction to Its Methodology (2nd ed.). Thousand Oaks, CA: Sage; 2004.

[33] Patton MQ. Qualitative Research and Evaluation Methods. London: Sage Publications; 2002.