The HOPE Trial and SMART Study (NCT03022032)

PI: Alexi A. Wright, MD, MPH

Dana-Farber Cancer Institute

IRB-Approved Protocol #16-477 (version 8.0)

April 23, 2021

Protocol Organization for DF/HCC Protocol 16-477

The protocol document contains the study procedures for the HOPE Trial and the SMART Study. The SMART Study is a sub-study of the HOPE Trial. Both studies evaluate *an almost identical intervention* using a Fitbit device and smartphone app(s) with the goal of improving quality-of-life for women with gynecologic cancers. However, the studies are designed to assess different research questions, and there are slight variations in the interventions being administered: the HOPE Trial is a randomized controlled trial designed to test changes in health-related quality of life at an NCI-designated Comprehensive Cancer Center (DFCI), while the SMART Study is a single-arm study designed to test the feasibility and acceptability of a combined intervention (Fitbit device and two smartphone apps) in NCORP community oncology sites.

Because the interventions tested are similar and only minor variations exist in study procedures (e.g., in timings of outcomes assessments), the studies are being reviewed under one IRB protocol at Dana-Farber Cancer Institute.

The HOPE Trial is being conducted only at Dana-Farber Cancer Institute. *No outside sites are participating in the HOPE Trial.* The HOPE Trial (Phase 2) is a four-arm randomized controlled trial testing Fitbits and a smartphone app. The primary endpoint of Phase 2 of the HOPE Trial is health-related quality of life.

The SMART Study is being conducted only at outside community oncology sites*. Dana-Farber Cancer Institute is not enrolling patients in the SMART Study.* The SMART Study is a single-arm study testing a Fitbit and two smartphone apps (Beiwe and SMART). Primary endpoints for this study are feasibility and acceptability of the intervention in the community oncology sites.

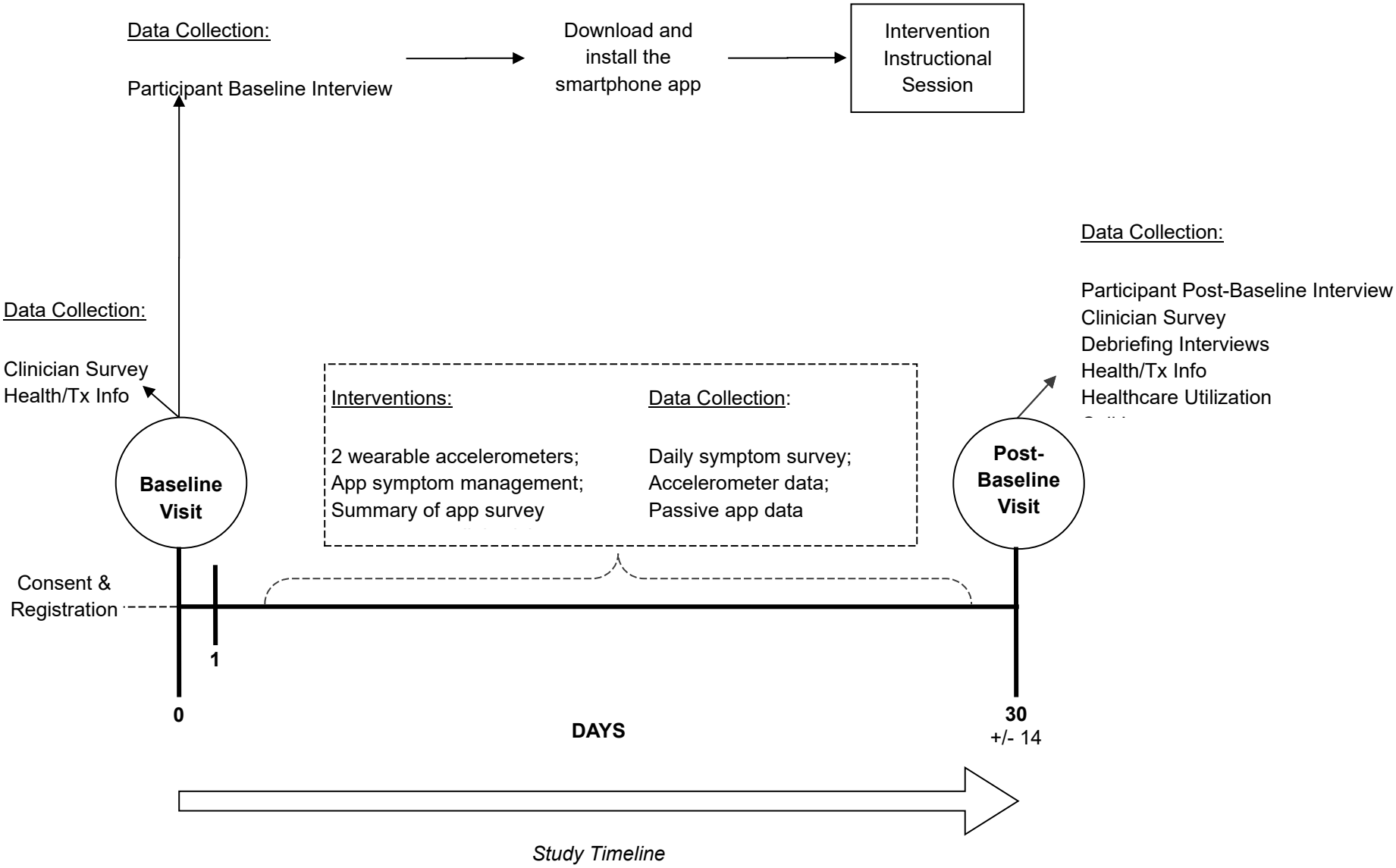
To facilitate protocol implementation and regulatory review at both Dana-Farber and outside sites, this document is separated into two sections. Part 1 is the protocol for the HOPE Trial conducted at Dana-Farber only; Part 2 is the protocol for the SMART Study conducted at community oncology sites only. Lettered appendices (Appendices A-Z and AA) correspond with the HOPE Trial; numbered appendices (Appendices 1-24) correspond with the SMART Study.

The HOPE Trial section begins on p.2 of this document. The SMART Study section begins on p. 41 of the document.

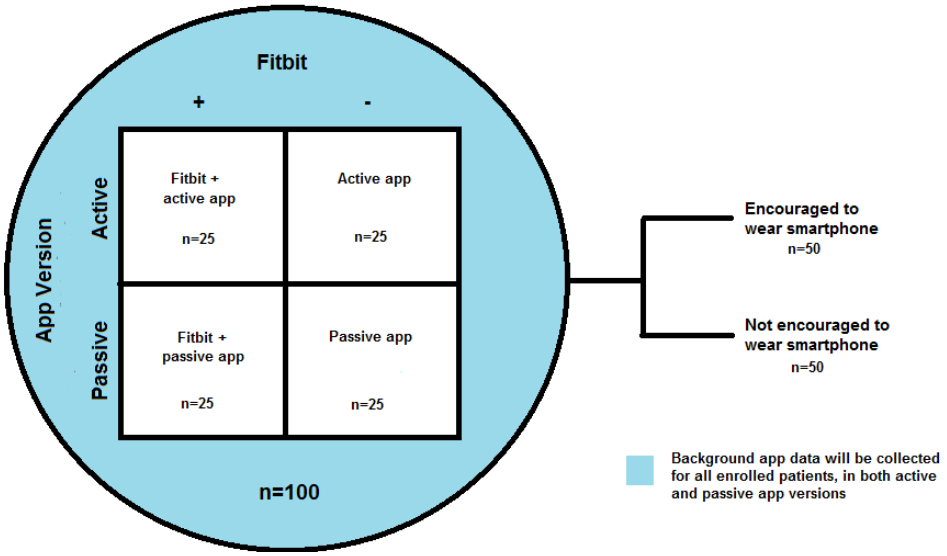
Part 1
The HOPE Trial

SECTION 1: Protocol Schema

First Phase: (n=10)



HOPE Trial Phase 2: Study Schema (n=100)



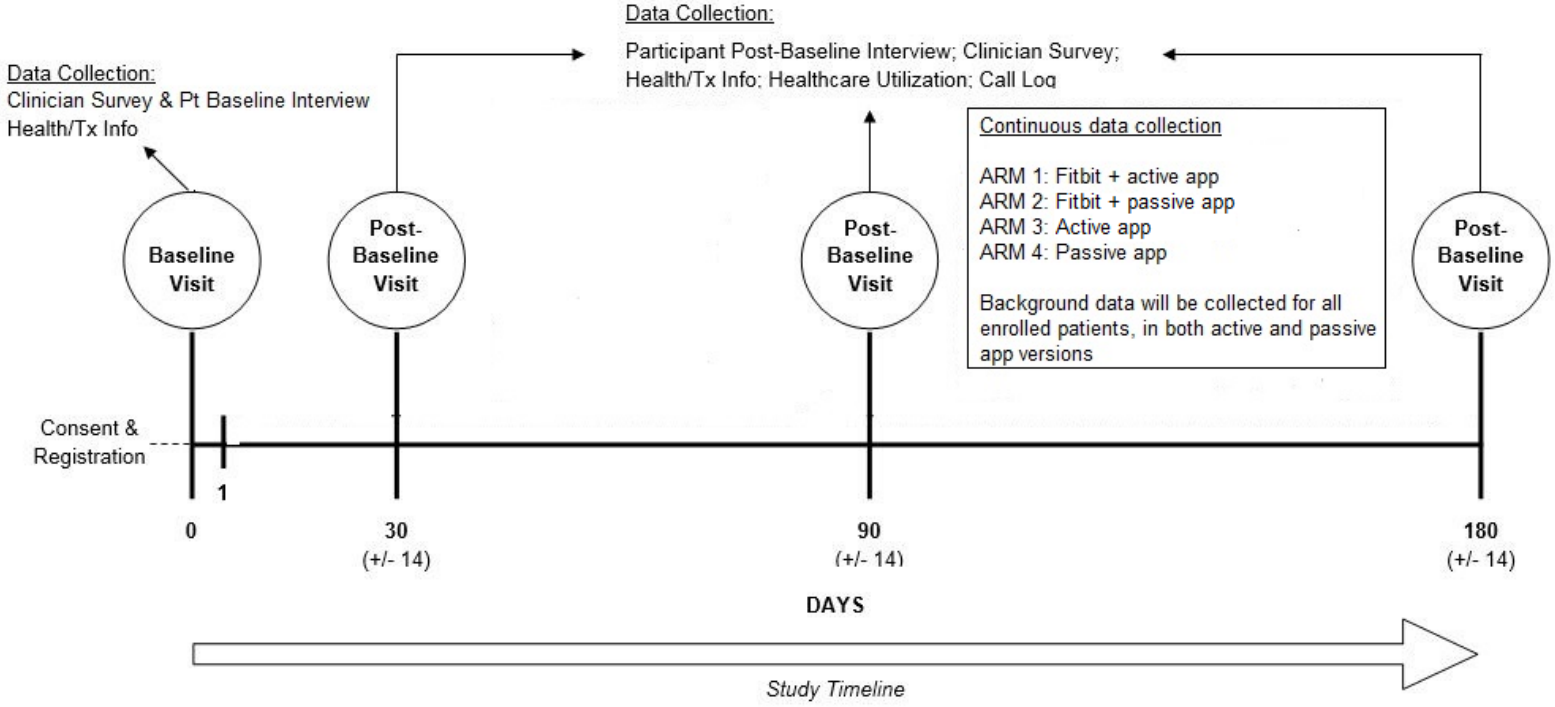


TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Overview

The goal of palliative chemotherapy is to reduce cancer patients' symptoms and extend survival. Yet, oncologists' methods of monitoring patients' symptoms are underdeveloped. Studies show that clinicians consistently miss more than half of cancer patients' symptoms, even in clinical trials that mandate collection of treatment toxicities.[1-3] This may be because clinicians see patients at fixed time points (e.g., every 3 weeks linked to chemotherapy infusions) when patients have already recovered from their last treatment. Additionally, patients may underreport symptoms in clinical settings or have difficulty estimating their activity levels, hindering oncologists' ability to accurately assess patients' symptoms and/or performance statuses. The moments between visits—when patients are at the highest likelihood of experiencing toxicities—are more likely to contain meaningful information about patients' symptoms and activity levels in the *real world*. Mobile health technologies (e.g., smartphones and accelerometers) offer novel methods for assessing patients' symptoms and activity levels and opportunities to intervene to reduce suffering.

The first goal of this study is to adapt and refine an existing smartphone app, paired with a wearable accelerometer, to assess patients' symptoms in a population of patients with gynecologic cancers receiving palliative chemotherapy. An existing app will be customized to collect patient-reported toxicities using the Patient Reported Outcome (PRO) version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and offer patients feedback about how to manage their symptoms. Patient symptoms will be risk-stratified. Patients with low-risk toxicities (grades 1 & 2) will receive tailored educational information, while patients with serious toxicities (grades 3 & 4) will receive alerts to call their clinician. Patients will also receive a graphical summary of their symptoms to share with clinicians during office visits. In first phase of the study we will conduct an initial assessment of the app with a diverse group of 10 patients to refine the app and test two different wearable accelerometers (i.e. Fitbit Zip and Fitbit Charge 2) before pilot testing. The wearable accelerometers will be used as a quantitative measure of patient performance status, and to detect severe symptoms that may impact patients' average daily steps (e.g., abdominal pain, nausea, diarrhea).[4] Patients will also be provided with a graphical summary of their average daily steps to share with clinicians.

The second goal of this study is to conduct a pilot randomized controlled trial (RCT) of the smartphone app and/or wearable accelerometer (i.e. Fitbit Zip or Fitbit Charge 2) to assess the feasibility, acceptability, and preliminary efficacy of our intervention. During the second phase of the study, we will conduct a 4-arm pilot RCT in 100 patients with gynecologic cancers receiving palliative chemotherapy to establish preliminary effect sizes. Participants will be randomized to: 1) Fitbit+active app, 2) Fitbit+passive app, 3) Active app, or 4) Passive app. We hypothesize that the use of a Fitbit and an active app designed to assess PRO symptoms and deliver tailored advice to cancer patients receiving palliative chemotherapy will reduce the use of high-intensity health care (i.e., unplanned infusion appointments, emergency room visits, and hospitalizations), compared with a Fitbit + passive app, Active app, or Passive app alone. We also hypothesize that patients randomized to the Fitbit + active app will have improved health-related quality of life (comparing the baseline and 6-month EuroQol EQ-5D), compared with other groups. Additionally, we expect that data collected from the wearable accelerometers and smartphone accelerometers (via passive app) will be significantly correlated with each other, and will provide quantitative measures that are correlated with patients' performance status.

We expect that the results of this pilot RCT, which is supported by the National Cancer Institute, National Palliative Care Research Center, and the Dana-Farber Cancer Institute Department of Medical Oncology, will provide a low-cost, scalable system to assess patients' symptoms, address low-risk toxicities, and alert clinicians when patients have toxicities that require intervention with the goal of reducing patient suffering and the use of high-intensity, hospital-based health care. Upon completion of this project, we will be well positioned to test the efficacy of this intervention in a full scale RCT.

1.2 Background and Rationale

There is substantial evidence that oncologists' miss up to half of cancer patients' symptoms, even within the context of clinical trials, which mandate structured reporting of symptoms and treatment toxicities.[1-3] Evidence suggests that the integration of PROs into routine cancer care results in more efficient symptom assessment,[5] improved communication and continuity of care,[6-8] better quality of life,[3,9,10] lower health care utilization rates,[10] and superior quality-adjusted survival, compared with usual care.[10,11] This is important because while prior studies have demonstrated that the early integration of palliative and oncologic care improves patients' quality of life and survival,[12-15] health systems are facing a serious workforce shortage of trained palliative care providers.[16] Low-cost, scalable systems designed to assess patients' symptoms, address low-risk toxicities, and alert clinicians when patients are in danger are urgently needed.

Several studies have demonstrated that cancer patients with serious illnesses are willing to report their symptoms using technology, including tablets and web-based systems,[10,17-19] even close to the end of life.[20] One large study of cancer patients found that nearly 70% of patients wanted to receive information and support about their disease through the internet.[21] Another demonstrated that the use of a web-based system to assess PROs in patients with advanced cancer, combined with automated clinical alerts, resulted in better health-related quality of life, fewer emergency room visits and hospitalizations, and superior quality-adjusted survival, compared with usual care.[22] Recently Denis et al. reported that the use of a web-based system to assess PROs weekly in patients with high-risk, non-small cell lung cancer resulted in earlier detection of symptomatic disease recurrences, earlier institution of supportive care, better patient quality of life, and improved overall survival, compared with routine clinical assessments.[11] Researchers have not examined similar endpoints in patients with gynecologic malignancies, to our knowledge, but one small study found that chemotherapy toxicity reporting was feasible in women with gynecologic cancers using a web-based system, and that use of this system improved patient recall of symptoms at follow-up visits, communication with physicians and nurses, and patients' self-efficacy.[17]

To date, however, most studies have focused on collecting patient-reported symptoms during clinic visits that are frequently tied to chemotherapy infusions. Two key limitations to this approach are: 1) patients have often already recovered from many treatment-related toxicities and 2) it relies upon patients' retrospective recall of events, which are often inaccurate. Few studies, to our knowledge, have performed *real time* and *real world* assessments of cancer patients' symptoms and activity levels in daily life.

Smartphone-based interventions are a low-cost, scalable tool for measuring and modifying health behaviors. In 2015, 64% of Americans owned a smartphone[23] and more than 33% reported relying upon it as their sole tool for accessing the Internet, particularly among low-income and racial/ethnic minority populations.[24] Mobile health interventions have demonstrated efficacy in assessing pain,[25] monitoring psychiatric diseases,[26,27] increasing medication adherence[28] and improving other important clinical outcomes (e.g., systolic blood pressure, and body mass index).[29]

Figure 1

Smartphones are capable of collecting two types of information: 1) "active data" which require patients' involvement (e.g., taking surveys; please see Figure) and 2) "passive data" which are collected without the patients' involvement (e.g., accelerometer data or spatial location).[30] One of the advantages of using smartphones is that they can leverage sophisticated surveying techniques to generate personalized assessments, eliminating questions that have a high likelihood of being irrelevant and therefore reducing the survey burden upon participants.[27] Smartphones can also be used to provide patients with real time active feedback for symptom management or to notify them that their symptoms are serious and require immediate attention.

To date, few studies have examined the use of mobile phone-based interventions in patients with cancer. Similarly, few have collected quantitative measurements of cancer patients' activity levels for extended time periods.[31-34] This study is innovative because it will harness a validated app, which is being piloted in psychiatric, neurological, and surgical patients in the Partners HealthCare system, to collect **passive** data from patients (e.g. accelerometer, spatial location, and sleep data) and **active** data, including patients' symptoms and treatment toxicities. The app has been tailored to categorize patient symptoms as low or high-risk, based upon clinical algorithms, and provide them with tailored advice to help manage their symptoms in *real* time in the *real* world. It is also innovative because it will enable clinicians to better understand patients' symptoms in the time between visits. We expect this study will increase the frequency of discussions about patients' symptoms between patients and providers. We also expect that this formative development work and early feasibility trial will set the stage for launching a broad portfolio of mobile-health intervention studies to improve seriously-ill cancer patients' symptoms, performance statuses, and clinical outcomes.

Like smartphones, wearable accelerometers (e.g. Fitbit Zip and Fitbit Charge 2) offer another novel means for collecting *real world* data to objectively measure patients' performance statuses. Patients' retrospective reports of activity levels are often inaccurate or imprecise. Without accurate information, oncologists may have difficulty objectively assessing patients' performance statuses, and may underestimate patients' symptom burdens and chemotherapy-related toxicities. Indeed, oncologist estimates of patients' performance statuses are only moderately correlated with one another[35,36] and weakly correlated with patient estimates,[37-39] but improve when clinicians and patients participate in "shared" reporting of patients' toxicities and performance statuses.[40]

Wearable accelerometers are devices that track users' energy expenditures, the amount and intensity of physical activity, and sedentary behavior. They offer cost-effective, user-friendly, and objective measurements of patients' free living patterns. A few studies have piloted wearable accelerometers in adult cancer patients undergoing stem cell transplants (HCT) or treatment for colorectal, gastrointestinal, breast, and lung cancers.[4,34,41,42] Results from one study of adult patients undergoing HCT who wore accelerometers over an 8 week period found that patients' reports of severe symptoms, impaired physical health, and restrictions in activities of daily living were associated with statistically significant decrements in objectively measured steps, suggesting that this may be an independent, quantitative measure of quality of life and patient performance status.[4] In this study of 32 patients undergoing HCT over a 4 week period patients' averaged 3,595 steps daily, and lower levels were significantly associated with an increased symptom burden.[4] Although similar estimates are not available in patients with gynecologic cancers, to our knowledge, we expect that symptoms are likely to impact the amount of walking that patients can do and will therefore provide an independent measure of both patients' performance status and symptom burden.

In the second phase of this study all patients will have passive data collected via the app. We will compare the active version of the smartphone app (which collects passive data, surveys patients about their symptoms, and provides tailored symptom management advice) alone or paired with a wearable accelerometer against a wearable accelerometer or control in a four arm RCT (see study schema). This will enable us to examine whether the active smartphone app and wearable accelerometer improve patients' quality of life, compared with active smartphone app or the wearable accelerometer, and determine whether their effects are independent or additive. In addition, it will help us determine whether wearable and smartphone-based accelerometers can provide valid and reliable measures of patient performance status and treatment toxicities.

2.0 OBJECTIVES

2.1 Phase 1

Objective: Adapt and refine an existing smartphone app to assess patients' toxicities and activity levels in 10 patients with metastatic gynecologic cancers receiving palliative chemotherapy and compare two wearable accelerometers (Fitbit Zip and Fitbit Charge 2) for use in the pilot RCT.

- Hypothesis: Patients will be able to successfully recharge the Fitbit Charge 2 every 3-4 days, but will prefer the Fitbit Zip because it does not require recharging.
- Hypothesis: The use of a wearable accelerometer will provide a quantitative measure that is correlated with patient performance status, and decrements of >25% in average daily steps will be associated with worse patient-reported quality of life and physical health (measured by the PROMIS Global-10 items 2 and 3).

2.2 Phase 2

Objective: Conduct a four-arm pilot randomized controlled trial (RCT) comparing the Fitbit + active smartphone app, Fitbit + passive app, Active app, or passive app alone to assess the feasibility, acceptability, and preliminary efficacy of the intervention.

- Hypothesis: Use of a monitored wearable accelerometer/passive smartphone app will improve patients' health-related quality of life (comparing the baseline and 6-month EuroQol EQ-5D), compared with passive smartphone app alone.

- Hypothesis: Use of both the active smartphone app and a monitored wearable accelerometer will improve patients' health-related quality of life (comparing the baseline and 6-month EuroQol EQ-5D), more than the active smartphone app or wearable accelerometer/passive smartphone app alone.

- Hypothesis: Use of the active smartphone app and a monitored wearable accelerometer will reduce the use of high-intensity health care (i.e., unplanned infusion appointments, emergency room visits, and hospitalizations), compared with a monitored wearable accelerometer/passive app, active smartphone app, or passive app alone.

- Hypothesis: Use of the active smartphone app will decrease the number of patient phone calls and/or for symptoms, compared with a wearable accelerometer/passive app or passive app alone.

- Hypothesis: Patients' and oncologists' estimates of a patient's performance status will be more closely correlated in patients randomized to the monitored wearable accelerometers/passive app compared with the active smartphone app alone or the passive smartphone app alone.

- Hypothesis: Data collected from the wearable accelerometers and smartphone accelerometers (via passive app) will be significantly correlated with each other, and will provide quantitative measures that are correlated with patients' performance status and will be predictive of clinically significant events (hospitalizations, emergency department visits, and chemotherapy appointments)

- Hypothesis: The correlation between the wearable accelerometers and smartphone accelerometers (via passive app) will be higher in patients randomized to be encouraged to wear their smartphone at all times, and the predictive ability of the smartphone accelerometers for patients' performance status and

clinically significant events will be greater in in patients randomized to be encouraged to wear their smartphone at all times.

- Hypothesis: Participants will express more negative affect and anxiety related to their cancer experience in the weeks preceding scans, compared with the weeks when scans are not performed. This association will be moderated by participants' coping style (as measured by the brief COPE).

3.0 RESEARCH SUBJECT SELECTION

3.1 Eligibility Criteria

Eligible patients include women >20 years of age who plan to receive chemotherapy at DFCI to treat recurrent, incurable gynecologic cancers (i.e., ovarian, uterine, and cervical that has recurred despite ≥1 prior treatments), own a smart-phone (Android or iOS), are capable of downloading and running the study app, can read and provide informed consent in English, and do not have cognitive or visual impairments that would preclude use of the app.

3.2 Exclusion Criteria

Patients will be ineligible if they are participating in an investigational drug treatment trial that requires structured symptom or toxicity reporting at the time of enrollment. Patients with severe cognitive impairments or who appear too weak, emotionally distraught, agitated or ill to participate, as judged by either the research study staff or an oncology provider, will be excluded. Patients who are unable to provide informed consent in English will be excluded because the smartphone app intervention is only available in English at this time. Children and young adults up to age 20 will be excluded because the diagnosis of metastatic gynecologic cancers in this age group is rare and the proposed instruments are not designed for people of those ages. In addition, patients with a life expectancy of ≤6 months, as determined by their oncology providers, will be excluded since they cannot participate in all of the required data collection. Patients who are currently actively tracking their steps using wearable technology or smartphone apps will also be excluded.

4.0 RESEARCH SUBJECT ENTRY

4.1 Subject Recruitment and Enrollment

We will enroll patients from the DFCI Gynecologic Oncology Program. Study staff, gynecologic oncology providers, and members of the Gynecologic Medical Oncology Team will identify patients who may be eligible for the study. Prior to initiating recruitment, we will meet with the clinical staff, including oncologists, embedded palliative care physicians, nurse practitioners, program nurses, clinical research study staff, and social workers, to discuss and solicit feedback on the recruitment and enrollment procedures.

4.11 Screening & Recruitment

Prior to obtaining informed consent, study staff will review the electronic medical records of patients listed on the gynecologic oncology providers' clinic schedules to identify patients with metastatic, recurrent gynecologic cancers undergoing chemotherapy. These patients' medical records will only be reviewed to confirm this protected health information (PHI), and it will only be shared with gynecologic oncology providers in the context of patients' eligibility for the study.

When an eligible patient is identified, study staff will contact the patient's oncology provider to confirm she meets the eligibility criteria and to request permission to approach the patient at an upcoming clinic visit. If the patient is approved to approach for enrollment, the research assistant (RA) will coordinate with the oncology provider to meet with the patient to discuss the study at the time of her clinic visit. If the

oncology provider deems the patient ineligible or too distressed to participate in a clinical study at this time, the patient will not be approached for inclusion.

PHI will not be shared with anyone outside of the study team and patients' oncology providers. All emails will be sent within the Partner's firewall. A HIPAA waiver requesting permission to review the PHI of these select patients prior to consent during screening and recruitment has been submitted to justify this process.

4.12 Informed Consent

If a patient agrees to learn more about the study, the RA will meet with the patient to describe the study, review the consent form, answer any questions, and provide her contact information. The RA will encourage patients to take their time in deciding whether they want to participate in the study or not.

If a patient is interested in participating, the RA will obtain written informed consent, which will include explaining how and why the current research study is being conducted, the study risks and benefits, the potential time commitment involved, and the option to give permission to be contacted for future research studies. The RA will explain in explicit detail what type of information will be collected from the smartphone application and wearable accelerometers and how these data are monitored. The RA will reiterate that the data collected are not a part of the patient's standard treatment and will underscore the importance placed upon maintaining patient confidentiality and a patient's rights while involved in the study, including the right to withdraw participation at any time for any reason during the study because participation is completely voluntary.

The informed consent form will contain a section dedicated to explaining what constitutes PHI and how this information will be protected as confidential per HIPAA guidelines. The consent form will also provide contact information for both the Principal Investigator (PI) as well as the Office for the Protection of Research Subjects. All informed consent processes will adhere to the policies set forth by the Institutional Review Board. Signed informed consent forms will be stored in a locked file cabinet to maintain the privacy of all study participants.

If a patient is unsure if she would like to participate in the study, she will be offered the consent form to review and a postage paid *opt-out card* (Appendix A) to notify study staff that she is not interested. If no contact is made after a few days, the RA will call the patient. If the patient decides to participate, the RA will meet her at a subsequent appointment to obtain informed consent. If a patient is not interested, the RA will thank her for considering, reassure the patient that the process will have no impact on her care. No further interactions will occur with patients who either decline or prove ineligible for the study. Patients will not be contacted after three unreturned voicemails.

4.2 Subject Registration and Randomization

During both phase I and phase II of the study, the RA will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations will occur prior to beginning study interventions. Any participant not registered to the protocol before study interventions have begun will be considered ineligible and registration will be denied. An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin study interventions. Issues that would cause delays in interventions should be discussed with the Overall Principal Investigator (PI). If a participant does not receive study interventions following registration, the participant's registration on the study will be canceled. Registration cancellations will be made in OnCore as soon as possible. After obtaining informed consent, participants will be assigned a unique study ID and registered to the study in Redcap.

The following information will be recorded for each participant in the *Registration Form* (Appendix B):

- Name and telephone number of RA enrolling the participant
- Date participant signed consent and RA who obtained consent
- Participant's study ID and first and last initials
- Participant's date of birth
- Participant's primary oncology providers
- Confirmation that participant meets eligibility criteria
- Name of oncology provider who approved participant's eligibility and date of approval
- Participant's contact preferences (phone call, text, or e-mail; collected post-consent)
- Participant's study arm (to be completed after randomization)

In the second phase, the study team will randomize enrolled participants to one of the four arms: 1) Fitbit+active app, 2) Fitbit+passive app, 3) Active app, or 4) Passive app —using a 1:1:1:1 ratio using a computer-generated random allocation sequence with blocks of 8 in order to maintain balance between study arms over time. Study staff will generate group assignments in sequentially numbered and sealed opaque envelopes. Please refer to the protocol schema for details.

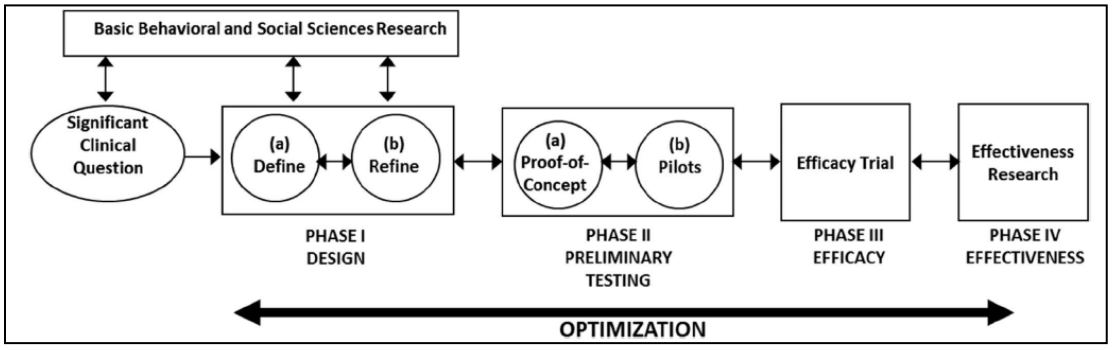
5.0 STUDY DESIGN AND METHODS

5.1 Design/Study Type

5.11 First Phase:

Ten patients will be purposively sampled to enroll a diverse group based upon guidelines for the Phase Ia and Ib of the Obesity-Related Behavioral Intervention Trials (ORBIT) model for behavioral treatment development (Figure 2).[43] In the first phase, we will enroll at least 3 patients who are ≥65 years of age, 3 patients from racial/ethnic minority groups, and 2 patients who do not use text messages to communicate >1x/week based upon evidence that patients with computer experience are more receptive to electronic self-reporting than those without experience.[44]

Figure 2



We anticipate enrolling 10 patients to refine the HOPE App intervention and determine which accelerometer (Fitbit Zip and Fitbit Charge 2) will be used in phase II of the study. In this phase of the study all participants will receive the smartphone app, the Fitbit Zip, and the Fitbit Charge 2 so that we can: 1) identify which wearable accelerometer to use in the second phase, and 2) compare step counts between the accelerometers (the smartphone, a hip-worn device, and a device worn on the non-dominant arm).

5.12 Second Phase

A feasibility and acceptability study will employ convenience sampling from 100 consecutive patients who meet inclusion criteria in a pilot randomized trial of:

Arm 1: Fitbit + active app
Arm 2: Fitbit + passive app
Arm 3: Active app
Arm 4: Passive app

There are two versions of the HOPE smartphone app—"active" and "passive." The "active" smartphone app refers to the version of the smartphone app in which active symptom collection is occurring (e.g, patients are receiving surveys and receiving tailored symptom management advice) in addition to passive data collection (accelerometer, GPS. Incoming calls and texts, etc.) The "passive" smartphone app refers to the version of the smartphone app in which only passive data collection is occurring, and no surveys or active data collection are being sent to participants. In the passive app, participant interaction with the smartphone app consists of installing the app and keeping it running in the background of their phone; all data is collected in the background. The active and passive apps are built on the same underlying platform and the security protections for the active and passive smartphone apps are identical, detailed in Appendix L, HOPE App Data Privacy and Security.

All patients will be assigned to a separate, secondary randomization either to be encouraged to wear their smartphone on them at all times, or not to be encouraged to wear their smartphone at all times (refer to study schema for details.) We have no reason to believe that encouragement to wear a smartphone will impact patients' health-related quality of life, performance status, and use of high-intensity health care/phone calls; thus, the secondary randomization will not impact the comparison of the 4 study arms for these outcomes.

With a total sample size of 100 patients (25 patients per arm), this study design will yield 70% power to detect a 6-point change in EQ-5D and 80% power to detect a 7-point change in patients' health-related quality of life (measured with the EQ-5D; see section 6.0). Our analyses will also provide preliminary estimates of feasibility, acceptability, safety outcomes, scale scores, missing data, and participant and physician feedback.

5.2 Selection of Instruments

5.21 Interviews and Surveys

The following measures will be used in the study interviews and surveys, including the *Participant Baseline Interview* (Appendix C), *Participant Post-Baseline Interview* (Appendix D), *Clinician Survey* (Appendix E), and *Symptom Survey* (Appendix F). Table 1 outlines their distribution across the study instruments.

5.21a Global Health Status: EQ-5D-5L

The EQ-5D is a standardized measurement of health status that has been used in a wide range of health conditions and treatments, including cancer patient populations.[45] The EQ-5D-5L is the most recent 5-level version that has proven validity and reliability in a range of patient groups with chronic diseases[46] and cancer.[47] It is a 5-item questionnaire (measuring mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. Each dimension has three levels of perceived problems: 1) no problems, 2) slight problems, 3) moderate problems 4) severe problems, and 5) extreme problems. Patients check the statement level that best describes their current health status in each dimension, which are then scored to generate a patient's unique health state. In the EQ-VAS, patients report a single index value of how good or bad their current health state is on a visual scale that ranges from worst imaginable at zero to best imaginable at one hundred. The EQ-5D-5L can be administered with little to no guidance and takes only a few minutes to complete. Upon scoring, the EQ-5D produces a composite score between 0-1 (multiplied by 100 to generate a number between 0-100), which represents general health status, normalized for the US population.[48] Lower scores represent worse quality of life, and a change of ≥6 is clinically significant in US cancer populations.[49]

5.21b PROMIS Global-10 and PROMIS Physical Function short form 6b

The PROMIS Global-10 is a brief measure of patient health status that is not disease specific.[50,51] It consists of 10 questions; e.g. "In general, how would you rate your physical health?" Items are scored on a Likert scale of 1-5, where higher scores indicate better health, except for pain which is measured on a 10 point scale. Standardized T-scores (range 0-100) are calculated for the global physical and mental health scales, and higher scores indicate better health. The full scale takes approximately 2-3 minutes to complete and will be used at baseline, post-baseline survey and the single-item global quality of life and physical health questions will be used daily among those randomized to the smartphone app.

The PROMIS Physical function (PF) 6b is a brief, 6 item measure used to characterize patients' overall health, level of physical disability, and general well-being. The PROMIS PF 6b has been validated in 4,840 cancer patients across a range of ages, racial/ethnicity groups, stages and cancer types, and normalized for the US population. It has high reliability, minimal floor effects, and can precisely measure meaningful differences in functional status, disease burden, and comorbidities.

5.21c Performance Status: ECOG PS

The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) assessment is a standard measurement that oncologists often use to assess a patient's current functional level and eligibility for clinical trials. The scale ranges from 0 to 5 and the criteria for each grade is as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; 3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4 = Completely disabled; cannot carry on any self-care; totally confined to bed or chair; 5 = Dead.[52]

The ECOG PS will allow clinicians and participants to provide a standard evaluation of the participant's performance status over time and with minimal burden. Participants will use the patient self-report version that has been used successfully in a study with cancer patients. We expect that it will take 1-2 minutes to answer the question.[53]

5.21d Depression: PHQ-9

The Patient Health Questionnaire-9 (PHQ-9) is a validated self-report measure that assesses nine depressive symptoms using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for major depressive disorder. It is used to screen, diagnose, and monitor depressive symptoms[54] and has been administered/demonstrated validity in cancer patients,[55,56] as well as smartphone apps.[27] Respondents report if each symptom has bothered them "not at all," "several

days," "more than half the days," or "nearly every day" during the previous two weeks.[57] We expect that it will take participants no more than 3-5 minutes to complete.

5.21e Symptoms Assessment: CTCAE and PRO-CTCAE

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-centered, standardized self-report measure that enables patients to report symptoms and AEs. Clinicians will use the standard CTCAE items (used to rate and report toxicities in therapeutic drug trials) while participants will use the PRO-CTCAE items. Dr. Schrag, one of the study's investigators, was one of the first researchers to identify, develop, test, refine and validate methods for collecting PROs.[17-19,22] She was instrumental in the development of the primary study measure, the PRO-CTCAE, which demonstrated favorable validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment.[19] Ten PRO-CTCAE items that are salient to gynecologic cancers will be collected, including: abdominal pain, nausea, vomiting, constipation, diarrhea, peripheral neuropathy, anxiety, depression, dizziness and fatigue.

The PRO-CTCAE items use conditional branching for AEs that contain multiple attributes. For example, if a participant reports a symptom, she is asked to quantify the severity and the extent to which the symptom interfered with her daily activities; if she does not report a symptom, these items are skipped. We anticipate that participants and oncology providers will complete their respective versions of the measure in about 3-5 minutes. Participants enrolled in phase I, and intervention arms 3 and 4 in the second phase RCT will also report their symptoms weekly in the HOPE app intervention.

5.21f Anxiety: GAD-7

The Generalized Anxiety Disorder 7-Item (GAD-7) is a reliable and validated self-report measure that assesses GAD. Respondents rate how often they have been bothered by 7 anxiety symptoms over the past two weeks using the following scale: 0 = Not at all; 1 = Several Days; 2 = Over half the days; and 3 = Nearly every day. Respondents also answer a question to assess the duration of their anxiety symptoms. Responses are tallied and the total score indicates the presence and severity of GAD.[58]

The measure has since been validated in the general population[59] and was the recommended evaluative measure for anxiety in adult cancer patients in the 2014 American Society of Clinical Oncology (ASCO) Guideline Adaptation.[60] We anticipate that it will take participants approximately 3-5 minutes to complete.

5.21j Overall Quality of Life and Physical Health: FACIT-PAL

Patients' quality of life (QoL) will be assessed with Functional Assessment of Chronic Illness Therapy – Palliative Care, which has demonstrated internal consistency, reliability and validity.[68] The measure is divided into four primary QoL domains: physical well-being (7-items), social/family well-being (7-items), emotional well-being (6-items), and functional well-being (7-items). It also includes 12 additional items that are specific to palliative care priorities for patients with chronic illnesses such as cancer. Participants will rate each symptom over the past 7 days as: 0) Not at all; 1) A little bit; 2) Somewhat, 3) Quite a bit, and 4) Very much. Subscales can be analyzed separately or aggregated to produce a total score.

5.21k Literacy Measures: Health Literacy and Numeracy & Mobile Communication Competence

Health literacy[69] and numeracy[70] and mobile communication competence[71] will be collected for all participants at baseline. The "comfort with technology" and "mobile preference" subscales of the Mobile Communication Competence scale will be used because they assess factors directly impacting patients in our study, who will be asked to acclimate to and consistently use an accelerometer and/or

smartphone app. The mobile communication preference and comfort with technology subscales individually demonstrated internal reliability, consistency and validity. We estimate that it will take participants approximately 5 minutes to complete all of the literacy measures.

5.21l Demographic Information

Basic demographic information will be collected for all participants, including: age, marital status, race/ethnicity, education, household structure, income, and employment. The questions will only take a few minutes to complete.

5.21m Smartphone Usage Questions

Data on smartphone-specific usage habits will be collected for all participants. Participants will be asked a total of four questions: average daily time spent using smartphone, purpose of using smartphone, comfort using smartphone apps, and frequency of using smartphone apps. We estimate that it will take participants approximately 2 minutes to complete these questions.

5.21n Cancer Experience Question

About the cancer experience question

On a weekly basis, participants will be asked one qualitative question about their cancer experience. We hope that this open-ended question will give patients an opportunity within the study to express additional concerns, emotions and experiences regarding their cancer that may not be adequately reflected in other study instruments. A large body of previous work has successfully asked cancer patients to share open-ended, qualitative measures of their emotional experiences (i.e. by writing in response to a prompt).[87-91] However, to our knowledge, our study will be the first to examine whether these qualitative measures correspond with clinical outcomes measured in real time in the real world.

Using a question adapted from Stanton and colleagues' emotional expression study with breast cancer survivors,[72] participants will be asked to describe their experience with cancer over the course of the previous week. Participants will be presented with the cancer experience question as an audio survey within the HOPE App once a week (see Appendix F for question text) and will record their answers into the microphone of their smartphone. The app reminds the participant to make a voice recording in the same way that it reminds the participant to take any other survey in the HOPE app: by making a notification appear in the phone. The participant does not need to make a voice recording immediately and may wait until she is in private to do so. The participant can make the audio recording in the app at any time after the notification appears, until the next audio recording reminder replaces it. Participants will spend up to 5 minutes on this question, depending on how much they wish to share. This question will be answered within the smartphone app at the baseline interview and symptom survey (once weekly).

Audio recording data security

Patients will be informed about the audio recording questions in the study in the consent form and during the informed consent process and will be encouraged to ask any questions they may have about the audio recording.

In the weekly audio recording questions, the participant's voice is recorded as an MP4 audio file so that researchers can analyze the audio file. The app's voice recording feature does not ask for any identifiable information, but it is conceivable that, in the course of describing his/her day, a participant

could speak his/her own name or reveal other identifying details. As such, the voice recording data is encrypted.

For all data except voice recording data, the app encrypts the data line-by-line as it writes data to the device's disk. This means that the app never writes unencrypted data to disk for these files. For the voice recording file, it is not feasible to do on-the-fly asymmetric encryption (since most of the established stream ciphers use symmetric encryption), so the voice recording file is encrypted once the recording is complete. Because the phone cannot decrypt any of its own data, when the participant views his/her survey answers, the participant is actually logging in to the server, downloading the answers via an SSL connection, and effectively viewing them through an HTTPS site, not decrypting any data on the phone.

The HOPE App will employ the same data privacy and security processes used in six IRB approved protocols across three Partners Institutions (BIDMC Protocol #: 2015P-000240; McLean Hospital Protocol #s: 2015P001303, 2015P001538, 2012P000890, 2015P002189; MGH Protocol #: 2015P000666). This list includes IRB-approved research studies that have also used the voice recording component of the app with patients as research participants. Although the app collects a large amount of data, it was custom built to be used in a health care setting and includes robust security and privacy features to safeguard all data and protect participants' privacy, including data anonymity, participant authentication, and data encryption.

Recordings will be tied only to a study ID number, and the only document linking the patient's study ID to identifiable information is in a restricted-access, password-protected file stored securely on Dana-Farber servers. Audio recordings from the HOPE App will be transcribed for further analysis using a DFCI-approved, HIPAA-compliant transcription vendor. All patient identifiable information will be removed when the audio recordings are transcribed. Audio recordings will be destroyed when analyses are complete.

Cancer experience question analysis plan

We plan to analyze qualitative data from the cancer experience question using the Linguistic Inquiry and Word Count (LIWC) program,[92] developed by James Pennebaker and colleagues and used widely in emotional expression literature with cancer patients and other populations.[87-90, 93] LIWC reads text and identifies which words are associated with psychologically-relevant categories, i.e. affect, cognitive processes, content dimensions, etc.[94] Because the holistic nature of the responses may not be adequately captured by the word count approach of LIWC analyses, we also plan to perform a content analysis[93, 96-97] of the output from the cancer experience question with trained independent raters, examining categories of psychologically relevant content in the recordings. For Phase I, due to the limited sample size, analyses will be descriptive in nature. For Phase II, we plan to use multivariate analyses of covariance (MANCOVA) as primary statistical procedures, controlling for baseline values, on conceptually related groups of variables including physical health-related outcomes (i.e., symptoms and healthcare utilization), psychological adjustment as measured by other study instruments (i.e., quality of life and emotional acceptance), and psychological properties of participants' responses to the cancer experience question (i.e. positive and negative affect). We also plan to conduct preliminary multivariate analyses of variance for continuous variables and chi-squared analyses for categorical variables, on demographic variables, cancer-related parameters, and other relevant variables (e.g quality of life) at baseline. If relevant, we will use the baseline values on these measures as covariates to control for nonsignificant chance variation between groups at baseline.[72]

5.21o Brief COPE

The Brief COPE is a 28-item measure developed to assess a broad range of coping responses.[91] The Brief COPE has been validated in several populations including breast cancer patients and community samples.[91] Subscales of the Brief COPE include use of emotional support, religion, and self-distraction, and individual subscales can be used independently. We will use the denial, behavioral disengagement, self-distraction, active coping, use of emotional support, use of instrumental support, positive reframing, planning, acceptance, and religion subscales of the Brief COPE. The Brief COPE will be administered to patients during the participant baseline interview (Appendix C).

5.21p Note on Smartphone Surveys

The PHQ-9 is not administered through the smartphone application—only during baseline and post-baseline surveys, which are administered by a research assistant—so the study team will become aware of any concerning responses to PHQ-9 items immediately. We will review the symptom surveys administered over Beiwe daily and have developed an automated internal reporting tool for this purpose. The audio recordings will be reviewed at the end of the study, and patients will be notified that the recordings will not be reviewed in real-time by a clinician when they are taught how to use the smartphone app. Additionally, after each symptom survey, patients are automatically reminded that a clinician will not see their responses in real-time and that they must contact their clinicians with concerns.

Table 1. Distribution of measures during Phase 1 and Phase 2

		INSTRUMENTS[1]					
		Participant Baseline Interview		Participant Post-Baseline Interview		Clinician Survey	Symptom Survey
		Phase 1	Phase 2	Phase 1	Phase 2		
MEASURE	PRO-CTCAE	✓	✓	✓	✓		✓
	PROMIS Global-10 and Physical Function 6b	✓	✓	✓	✓		✓
	CTCAE					✓	
	ECOG PS	✓	✓	✓	✓	✓	
	PHQ-9	✓	✓	✓	✓		
	GAD-7	✓	✓	✓	✓		
	EQ-5D-5L	✓	✓	✓	✓	✓	
	FACIT-PAL	✓	✓	✓	✓		
	Brief COPE		✓				
	Health Literacy & Numeracy	✓	✓				
	Cancer Experience Question		✓				✓
	Mobile Communication Competence	✓	✓				
	Smartphone Usage Questions	✓	✓				
	Demographic Info	✓	✓				

[1] Measures were refined during phase I, resulting in the addition or omission of instruments in response to patient or physician feedback

5.22 Medical Chart Abstractions and Patient-Reported Medical Resource Utilization

5.22a Health/Treatment Information

Participants' medical charts will be reviewed to abstract health and treatment related information, including disease site, comorbid health conditions,[73] number of prior chemotherapy regimens, and time since diagnosis. Data will be recorded in the *Health/Tx Info* form (Appendix G).

5.22b Health Care Utilization

Participants' medical charts will be reviewed to abstract health care utilization data during enrollment, including chemotherapy regimen and treatments, palliative care visits, emergency department visits, hospitalizations, and hospice referrals. If a participant dies while enrolled in the study, the date of death will also be recorded. Data will be recorded in the *Health Care Utilization* form

(Appendix H). Participants will also be given a patient diary to record all health care utilization that occurs during the study period, including hospitalizations, admissions to an intensive care unit, emergency room and urgent care visits, and oncology visits. This form was developed by the NRG Cancer Care Delivery Research Group because of a recognition that participants often receive care at outside hospitals that cannot be captured by abstracting the medical record. Clinical research coordinators will be asked to verify medical care that happened within a site-affiliated medical center. Participants' medical charts will be reviewed to abstract health care utilization data during enrollment, including chemotherapy regimen and treatments, palliative care visits, emergency department visits, hospitalizations, and hospice referrals. If a participant dies while enrolled in the study, the date of death will also be recorded. Data will be recorded in the Medical Resource Utilization Form (Appendix Z). Additionally, participants will be asked about whether they (or their informal caregiver) needed to take time off from work, how far they traveled for treatment, and for a rough estimate of their out-of-pocket expenditures to capture some of the burden associated with cancer care.

5.22c Call Log

Per usual care, program nurses in the Division of Gynecologic Oncology will document participants' phone calls with clinical staff in participants' electronic medical health records. Study staff will abstract information about these phone calls during a participant's enrollment and record data in the *Call Log* (Appendix I). Data collected for each call will include: date/time, incoming/outgoing, left message, duration in minutes, reason for the call, symptoms documented, and the outcome.

5.23 Debriefing Interviews

Debriefing interviews will be conducted with participants enrolled in the first phase and their oncology providers. The purpose of these interviews is to obtain information about the acceptability of the interventions and recommendations for modifications to improve any aspect of recruitment, enrollment, education, timing of study assessments, and the graphical display of information, the wearable accelerometers, and the smartphone app. We will also conduct debriefing interviews with a purposively sampled subset of patients enrolled in Phase II (see Appendix J: Debriefing Interviews for Phase 2). We will administer interviews to 5 patients enrolled in each arm of the study. We will aim to sample a subset of patients with varying backgrounds and experiences with the study in order to better understand how the HOPE trial interventions work across a diverse patient population.

Additionally, debriefing interviews will be audiotaped in order to ensure that the interviewer adequately captures all feedback from patients and caregivers. The consent forms for the study include information that the debriefing interview will be audiotaped, and we will verbally request permission from patients to audiotape the debriefing interview before beginning the interview. Verbal permission will be documented on RedCap in Appendix J: Debriefing Interviews for Phase 2. We will not administer a debriefing interview to any patient who does not consent to being audiotaped during the debriefing interview. All audio recordings of study sessions will be stored in secure locations in restricted-access, locked filing cabinets on Dana 10 and 11, and in password-protected folders on Partners servers. Recordings will be tied only to a study ID number, and the only document linking the patient's study ID to identifiable information is in a restricted-access, password-protected file stored securely on Dana-Farber servers. Audiotapes of debriefing interviews will be transcribed for further analysis using a DFCI-approved, HIPAA-compliant transcription vendor. All patient identifiable information will be removed when the audio recordings are transcribed. Audio recordings of debriefing interviews will be destroyed when analyses are complete.

5.3 Description of Interventions

Per the protocol schema, the first phase of the study will test the HOPE app with the Fitbit Zip or the Fitbit Charge 2. Based on the usability and acceptability data, the larger pilot RCT will test the HOPE app and the Fitbit model selected based upon user feedback. Based upon participant feedback (70% preferred Charge 2) from the first phase of the study, Phase II will test the HOPE app with the Fitbit Charge 2.

5.31 Monitored Wearable Accelerometer: Fitbit

The Fitbit Zip is a commercially available accelerometer that is worn on the hip and tracks users' steps, distance, calories burned, and active minutes. The accuracy of the step counts reported by Fitbit's hip-worn accelerometers have been validated against treadmill walking,[74] other accelerometers,[75, 76] and an indirect calorimetry device.[77] In addition, the Fitbit Zip was found to be the most valid device in a study that examined the validity and reliability of ten commercially available accelerometers for measuring step count against the gold standard devices used in laboratory and free-living conditions.[78] One of the advantages of the Fitbit Zip is it runs off of a watch battery which only needs replacing every 2-3 months. One of the disadvantages to using the device in free-living conditions is it may be difficult to distinguish between low activity levels and low adherence to the device.

The Fitbit Charge 2 is an accelerometer that is worn on the wrist and tracks users' heart rate continuously in addition to steps, distance, calories, and active minutes. The addition of an optimal heart rate sensor enables monitoring of the time that the tracker is being worn (e.g., adherence).[79, 80] Wrist-worn activity trackers have been shown to accurately measure heart rate when compared with electrocardiography,[81, 82] have good test-retest reliability (intraclass correlations of 0.75-0.95)[78] but over count steps compared with the gold standard ActivPAL in free-living conditions due to the variability in limb-specific activities.[83] One of the advantages of the Fitbit Charge 2 is it allows for close monitoring of adherence to the device over time because of its continuous measurement of heart rate. The disadvantages include: it is not as accurate as a hip-worn device, is dependent upon the user to recharge it every 3 days, and may be less accurate if the participant is dependent upon a device for ambulating (e.g., cane or walker) or wears the device on her non-dominant arm.

Fitbit data will be stored with Fitabase, (Small Steps Labs LLC), a third-party research platform designed to collect data from the Fitbit (https://www.fitabase.com). It provides minute-by-minute measures (e.g. steps, heart rate) for data monitoring and analysis.[82] All data will be anonymized with the use of participant codes, and the data will be stored a in high security data center. [82, 84]

5.32 Smartphone Application: HOPE App

The other intervention is an iOS and Android smartphone application that runs on participants' personal smartphones and collects information about their health and behaviors. Originally named "Beiwe," the app was conceived and designed by one of the co-investigators, Dr. Jukka-Pekka Onnela, at the Harvard T.H. Chan School of Public Health. Zagaran, Inc., located in Cambridge, Massachusetts, built the software.

In a prior pilot study, Dr. Onnela tested the app in 13 patients with major depressive disorder. Participants installed the app on their personal smartphones and completed a self-report survey of PHQ-9 items 3 times per day with >75% adherence to the app over a 30-day period[27]. Participants scores were strongly correlated with paper-based surveys administered in clinic (Pearson linear correlation coefficient 0.84) but were 3.0 points higher on average (i.e. indicating more distress), and participants were much more likely to report significant suicidal ideation.

Since this publication, Dr. Onnela's lab has developed a more sophisticated system that features a web-based research study portal, a customizable Android and iOS smartphone app, Amazon Web Services S3 database, and data modeling and analysis tools. The app collects many different types of sensor data and administers surveys. Although this platform has not yet been used in cancer patients,

there are currently 8 IRB approved protocols across local centers that are utilizing the Beiwe application in research, including Beth Israel Deaconess Medical Center, Harvard University (Faculty of Arts and Sciences), McLean Hospital, and Massachusetts General Hospital. Three studies have begun enrolling patients or healthy controls, and the user experience has been overwhelmingly positive. In addition, there are no signs that adherence is condition-specific to date.

In this study, the active smartphone app is named the "Helping Our Patients Excel (HOPE)" app.

5.32a. App Versions (Active vs. Passive)

The HOPE Trial will employ two different versions of the customized smartphone app: an "active" app and a "passive" app.

Active app: The "active" app collects **both active and passive data** from the participant's phone usage. Active data is collected while a patient is using the app (e.g. responding to survey questions). Passive data is collected continuously without patient input. Patients using the active app will be asked to actively respond to survey questions including the symptom survey and cancer experience question.

Passive app: The "passive" app collects **passive data only** from the participant's phone usage. It does NOT collect active data (e.g, the participant will not be asked to respond to any survey questions.) The passive data collection will occur in the background of the phone.

As noted above, both the active app and passive app collect passive data from the participant's phone. Specifically, as detailed in the *HOPE App Data Privacy and Security* (Appendix L), passive data includes: mobility traces, consisting of flights (linear segments of movement) and pauses (times of no movement) which are constructed from GPS data; and summary statistics of phone communication (calls and text messages) patterns, simple examples being the total number of communication events in a time period (e.g., 1 week), the total number of communication partners, reciprocity of communication (defined as the difference between outgoing communication volume and incoming communication volume).

The active and passive app are built on the same underlying platform (Beiwe). As such, the active and passive app have identical data security protections, which are detailed in Appendix L, HOPE App Data Privacy and Security.

5.32b Software and Data Collection Features

The smartphone apps employ the original features and data collection methods used in the aforementioned studies and protocols. Consult *HOPE App Features and Screenshots* (Appendix K) for descriptions of the app's features, including: log-in screen, "Call My Clinician" button, "Forgot Password" button, notifications, surveys, "Call Research Assistant" button, and main menu.

5.32c Symptom Management

The active smartphone app is designed to collect and assess participants' toxicities and symptoms on chemotherapy treatment in between visits with their clinician. Participants report the severity of their symptoms via a brief in-app survey of PRO-CTCAE items. The app then determines a symptom's risk level and necessary response, which is either to provide no intervention, tailored symptom management advice, or an alert to call the clinician. Figure 3 provides a more detailed overview of this process.

The symptom response criteria and the *Symptom Management Content* (Appendix M) were developed by research staff in cooperation with the gynecologic oncology providers and staff nurses at Dana-Farber. The study PI, who is also a practicing gynecologic oncologist on the gynecologic oncology team, collated reputable and trusted sources, such as ASCO, the National Cancer Institute, and Dana-Farber, to create the content for each symptom, which includes: symptom management advice and questions to ask the clinical team. The content and response criteria were then reviewed and refined by study investigators, research staff, and gynecologic oncology clinicians to produce the final versions.

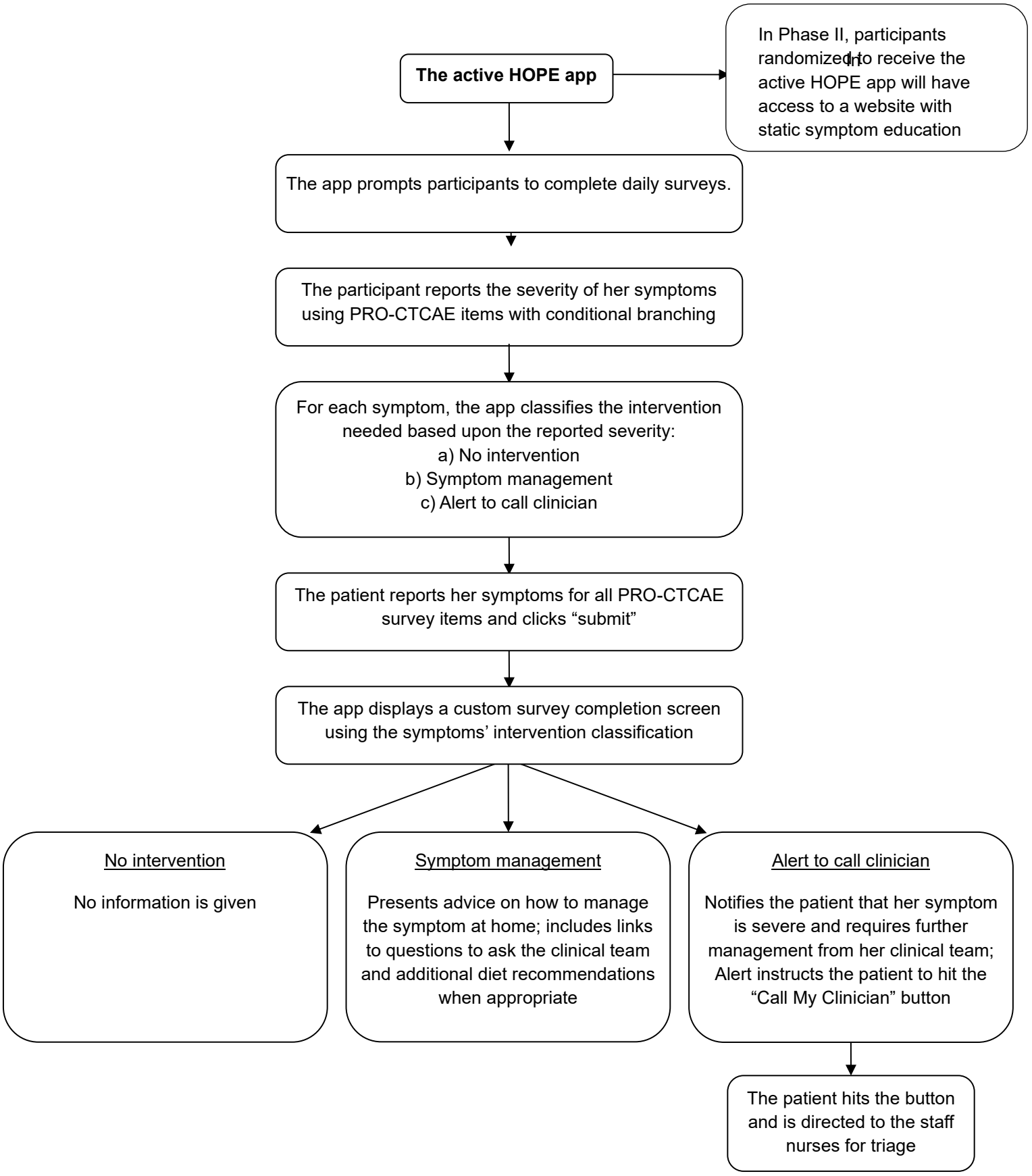
5.33 HOPE Symptom Education Website

In Phase II of the study, participants randomized to receive the Fitbit+active app, or active app arms will have access to a website (www.hopetrial.org) which will contain static patient education materials about the symptoms that are targeted in the HOPE app. This website will present evidence-based information on symptom education and symptom management. Some of the content on the website will mirror the content in the symptom management app, while other information will be housed only on the website. The purpose of the website is to provide a centralized location for patients to find symptom education and symptom management information at any time they might be experiencing low-level symptoms. Content will be created by the study PI (a practicing gynecologic oncologist at DFCI) and the study team, and will include information from trusted sources such as the NCI and ASCO.

5.34 Encouragement to Wear Smartphone

In Phase II of the study, participants will be randomized both to a main study arm and a secondary randomization. The secondary randomization will randomize patients either to be encouraged to wear the smartphone at all times during the study (n=50), or not encouraged to wear the smartphone at all times during the study (n=50). Participants who are randomized to the “encouraged” arm will receive an appliance (e.g belt clip/arm band) which will allow them to carry their smartphone with them throughout the day, including while they would not ordinarily carry their smartphones with them (such as when walking around inside the home.) Participants who are randomized to the “not encouraged” arm will not receive any instructions about keeping their smartphone with them, and will not be provided with an appliance to carry their phone throughout the day.

Figure 3. Symptom classification and response in the *active* smartphone app intervention



5.4 Data Collection

Tables 2 and 3 specify the instrument and intervention data collection timelines during each study phase. Intervention data will be collected continuously during enrollment; all synch automatically over Wi-Fi.

Table 2. First phase instrument data collection

		DAY		
		Visit 0	1-29	Visit 30
INSTRUMENT	Participant Baseline Interview	✓		
	Participant Post-Baseline Interview			✓
	Clinician Survey	✓		✓
	Debriefing Interviews			✓
	Accelerometer Data		✓	✓
	Daily QoL,PF, and Symptom Questions		✓	
	Weekly Symptom Survey		✓	
	Passive App Data		✓	✓

Table 3. Second phase RCT instrument data collection per study arm

		DAY						
		Visit 0	1-29	Visit 30	31-89	Visit 90	91-179	Visit 180
INSTRUMENT	Participant Baseline Interview	1,2,3, 4						
	Participant Post-Baseline Interview			1,2,3,4		1,2,3,4		1,2,3,4
	Clinician Survey	1,2,3, 4		1,2,3,4		1,2,3,4		1,2,3,4
	Health/Tx Info	1,2,3, 4		1,2,3,4		1,2,3,4		1,2,3,4
	Healthcare Utilization			1,2,3,4		1,2,3,4		1,2,3,4
	Call Log			1,2,3,4		1,2,3,4		1,2,3,4
	Accelerometer Data		1,2	1,2	1,2	1,2	1,2	1,2
	Daily Quality of Life, Physical Function, and Symptom Questions		1,3	1,3	1,3	1,3	1,3	1,3
	Weekly Cancer Experience Question	1,3	1,3		1,3		1,3	
	Weekly Physical Function Survey		1,3	1,3	1,3	1,3	1,3	1,3

1. Fitbit + active app
2. Fitbit + passive app
3. Active app
4. Passive app

Data obtained via interviews, surveys and chart abstractions will be stored on the Harvard REDCap server. HOPE App will employ the same data privacy and security processes used in six IRB approved protocols across three Partners Institutions (BIDMC Protocol #: 2015P-000240; McLean Hospital Protocol #s: 2015P001303, 2015P001538, 2012P000890, 2015P002189; MGH Protocol #: 2015P000666**)**. Although the app collects a large amount of data, it was custom built to be used in a health care setting and includes robust security and privacy features to safeguard all data and protect participants' privacy, including data anonymity, participant authentication, and data encryption. Hope App Data Privacy and Security describes the processes in detail.

Fitbit data will be stored with Fitabase, a research platform that collects and stores data from Internet connected devices, like Fitbit, for monitoring and analysis. It provides minute-by-minute measures (e.g. steps, heart rate) for data monitoring and analysis.[82] All data will be anonymized with the use of participant codes, and the data will be stored a in high security data center.[, 82,84]

5.5 Description of Study Process

Study procedures for the first phase are outlined below. Prior to opening the second phase, the study protocol and procedures will be amended based upon participant and clinician feedback. The RA will be primarily responsible for carrying out the following procedures; study staff will be trained accordingly so they can perform procedures as needed.

Based on the study team's experience conducting pilot studies, we understand that piloting minimal-risk interventions must be flexible in order to ensure that they can quickly adapt to patient needs as we learn more about them over the course of the study. The study activities currently outlined in the protocol therefore may be adapted without the submission of an amendment in cases where these modifications would pose no additional risk to patients, as determined by the study PI.

5.51 Instrument Administration

Participant Baseline Interview:

- The RA will administer the survey to participants via an in-person interview on Day 0 before or after the participant's visit with her oncology provider (Baseline Visit).
- Participants will complete the interview on the same day informed consent is obtained; if this is not possible, the RA and participant will plan to complete it at a subsequent visit.
- Participants will not be asked to come to Dana-Farber outside of their regularly scheduled visits.
- Estimated time to completion: 45 minutes.

Participant Post-Baseline Interview:

- The RA will administer the interview to participants via an in-person interview before or after a regularly scheduled visit that falls as close to the projected assessment date as possible (Post-Baseline Visit).
- Every effort will be made to administer the interview in-person and on the date of the Post-Baseline Visit. If this is not feasible, participants will complete it over the phone as close to the visit date as possible.
- To encourage participation and reduce the number of incomplete interviews, participants will be contacted prior to their visit to confirm the date of their upcoming visit and interview.
- Estimated time to completion: 30 minutes.

Clinician Surveys:

- The oncology provider(s) who met with the participant during the Baseline and Post-Baseline Visit will complete the survey.
- To help ensure surveys are completed in a timely manner, study staff will highlight their importance during study training and elicit clinicians' preferences for receiving and completing surveys, which will include: a HIPAA-compliant email, Redcap survey, hard copy, or in-person interview.
- The RA will administer the survey according to the provider's personal preferences within 24 hours of the visit. If not completed within 48 hours of receipt, she will leave a hard copy in the clinician's office or administer the survey during the weekly GYN research meeting.
- Estimated time to completion: 5 minutes.

Symptom Survey:

- Participants will be prompted by the HOPE app to complete the survey.
- The surveys will consist of single item measures of global quality of life and physical health, administered daily; the PROMIS PF 6b (6-item questionnaire about physical function) administered weekly; PRO-CTCAE questions for 10 symptoms, administered weekly (2 symptoms per day over 5 days); and a cancer experience question (audio recording), administered weekly.
- Survey items will not interfere with participants' use of their phone, but they will remain present until they are completed.
- Estimated time to completion: 3-5 minutes.
- At each subsequent visit, participants and their oncology providers will be given a summary of their survey responses since the last visit.

Debriefing Interview:

- The RA will conduct debriefing interviews with participants enrolled in the first phase and a subset of the patients enrolled in the second phase immediately following their completion of the final post-baseline survey (either in-person or over the phone).
- Study staff will discuss the debriefing interviews to identify opportunities for protocol improvement.
- Estimated time to completion: 5-10 minutes

Health/Treatment Chart Abstraction:

- The RA will review participants' medical charts to complete the Health/Tx Information form at the time of participants' baseline and post-baseline visits.
- Chart abstractions will be completed within 10 days of participants' study visits.

Health Care Utilization Chart Abstraction:

- The RA will review participants' medical charts to complete the Health Care Utilization form at the time of participants' baseline and post-baseline visits.
- Chart abstractions will be completed within 10 days of participants' study visits.

5.52 Intervention Administration

5.52a Smartphone App

Instructional Session (*passive and active app)*:

- Following the completion of the Participant Baseline Survey on Day 0, study staff will help participants download, install, and run the HOPE App on their personal smartphones.
- Participants will be prompted by Android or iOS to agree install the app and the software will review what the app will have access to on the phone (see the participant guide). This language is part of the Android and iOS operating systems and cannot be changed. There is no way to prevent this message, which is a basic security feature in Android and reflects the broadest possible access granted to an application.
- To ensure that subjects are not misinformed, the study staff member will explain the app's privacy and data security in the *HOPE App Required Reading & Discussion* document (Appendix N). It should be noted that the discussion related to access on page 3 is specific to Android phones only.
- When the app opens, participants will register using a unique User ID and temporary password and then choose a new password. The subject will be assigned a unique 8-character Participant ID which consists of mixture of numbers and letters. The app does not ask the subject to enter any personal information (name, date of birth, phone number, etc.) and cannot be directly linked to their DFCI health records.
- Participants will enter their oncology providers' phone numbers for the "Call my Clinician" button and enter the RA's contact number for the "Call Research Assistant" button.
- At the end of the registration process, the participant will click a button to acknowledge she has reviewed the information with the RA and provide in-app consent.
- The RA will then review how to use the app and participants will be given a copy of the *HOPE App Participant Guide-Active App* (Appendix O) or the *HOPE App Participant Guide—Passive App* (Appendix W) which describes the app and provides directions on how to use its features, frequently asked questions, as well a review of the data that is collected and privacy measures.

Symptom Management (*Active app only)*:

- Participants will be prompted to answer single item global measures of their quality of life and physical health daily; answer 6 questions about their physical function weekly; answer one question about their cancer experience weekly; and answer questions about 2 symptoms daily in between study visits via the HOPE App in the Symptom Survey (details in section 5.52).
- If a participant reports one or more low-risk toxicities, the app will present tailored advice on how she can manage each symptom at home. If participants report high-risk toxicities, they will be instructed that they have reported a toxicity that requires further management from their clinical team and to hit the "Call My Clinical Team" button. Please refer to the figure in section 5.53 for an overview of this process.
- After completing each survey, the app will remind participants that the results will not be reviewed by a clinician, so the survey cannot be used to communicate with study staff or to request help. The reminder will also note that if the participant feels unsafe, she should contact the treating clinician directly.

- At each clinic visit, participants and their oncology providers will be given a graphical summary of the symptoms participants reported, and/or the steps walked by participants (depending on study arm) in-between visits. The study team will provide a summary of symptoms and/or steps either by providing a hard copy during clinic or through email, depending on feasibility and provider preference. If the patient is randomized to the active app-only study arm, she and her provider will only receive symptom reporting; if the patient is randomized to the accelerometer+passive app study arm, she and her provider will only receive "step count" reporting; if the patient is randomized to the active app+accelerometer arm, she and her provider will receive both symptom and step count reporting; and if the patient is randomized to the passive app only study arm, she and her provider will not receive a symptom summary. This is dependent on patient adherence –e.g if a patient is not wearing her Fitbit or using the smartphone application and we are unable to receive step or symptom data, we will not have data to share with patients or their clinicians and no summary sheet will be provided. See Appendix V: Sample Summary Sheet for an example of what the summary data will look like. We will not monitor whether clinicians use the summary sheets, since it is difficult to reliably capture what providers read and absorb during clinic visits.

App Use and Compliance (*Active and passive app)*:

- Participants will be instructed to avoid adjusting the app settings to ensure data is collected. We will contact patients when we do not receive data from the app and/or Fitbit and aim to do so according to their contact preferences stated in the registration form.
- If the app is not synching properly, the RA will contact patients via text/phone/email to help resolve the issue remotely. If this is not possible, the RA will meet participants at a regularly scheduled clinic visit to download the data manually or help resolve the issue.

5.52b Wearable Accelerometers:

All participants will also receive a Fitbit Zip and Fitbit Charge 2. Participants in the Fitbit and Fitbit+HOPE App arms of Phase II of the study will receive only the Fitbit Charge 2.

Instructional Session:

- Following the completion of the Participant Baseline Survey on Day 0, the RA will help participants' download the Fitbit software and smartphone app, demonstrate how to use the Fitbit app and device, and teach patients how to synch the device to their smartphone. Participants will be assigned a unique study email that will be used to synch the device with the Fitbit app, as well as register the device in Fitabase (i.e., study's data collection platform).
- To reduce missing data, the RA will highlight the importance of wearing the accelerometer and review how they will be contacted by the study team, ideally through their preferred method of communication (phone/text/email), to encourage compliance. In addition to the accelerometer, participants will receive a wireless sync connector, and the *Fitbit Participant Guide* (Appendix Q), which describes proper wear and care, charging and battery life, troubleshooting instructions, uploading data, and compliance.
- The RA will encourage participants to contact study staff at any time with questions or issues to help ensure proper wear and use of the Fitbit.

Wear Time, Compliance, and Monitoring Average Daily Steps*:*

- Participants will be asked to wear the Fitbit Charge 2 on their non-dominant wrist. Study staff will continuously monitor participants wear time and data via Fitabase. We may contact patients when we do not receive data from the app and/or Fitbit and aim to contact patients according to their preferences stated in the registration form. If a Fitbit is not synching properly, the RA will contact patients via text/phone/email to help resolve the issue remotely. If this is not possible, the RA will meet the participants in person at a regularly scheduled clinic visit to download the data manually.

Tracking Devices:

- The accelerometers assigned to each participant will be tracked according to the product serial number and assigned unique ID number.
- Participants will be allowed to keep the accelerometers as a token of appreciation for their participation in the study, and to minimize potential transmission of skin infections (e.g. methicillin-resistant Staphylococcus aureus) between participants.

5.53 Special Concerns

5.53a Troubleshooting the HOPE App

The intervention's participant guides outline common troubleshooting issues and how to solve them. Participants will be instructed to call study staff as soon as possible to report if they are having trouble using the app.

5.53b Lost Accelerometers

If a participant reports to study staff that she lost the accelerometer, study staff will provide a replacement, either in person or via mail, as soon as possible.

5.53c Surveys

Study staff will contact participants to complete their upcoming study survey. After three unreturned voicemails, participants will not be contacted again for additional surveys.

5.53d Subsequent Enrollment in a Therapeutic Drug Trial

Participants in this study may enroll in a therapeutic drug trial at any point after signing consent to participate in this study. However, if a patient enrolls in a therapeutic drug trial that requires structured symptom or toxicity reporting we will record this and perform a sensitivity analysis, excluding any patients who participated in a therapeutic trial after enrollment, to determine whether this impacts our findings. Since this is a feasibility and acceptability trial, we do not want to censor participants.

5.54 Compensation

In the first phase, there will be no compensation for participants in this study. However, participants will be allowed to keep the wearable accelerometers (approximately $200 value) and will be provided with phone chargers to compensate for battery drainage that may be caused by installing the HOPE App (approximately $15 value). In the second phase, participants who are randomized to the corresponding arms will be allowed to keep the wearable accelerometer and/or receive a phone charger if requested. All

patients will be provided with a gift-card after the 1-month, 3-month, 6-month interviews to minimize attrition and prevent differential drop-out by study arm. The incentives will be $20 at 1 month, $30 at 3 months, and $50 at 6 months. Subjects who are randomized to arm 4 (passive app) will also receive a $20 gift card after the first study interview at baseline.

In addition, if subjects incur additional costs related to their phones' data plan use as a result of participating in the study, subjects will be asked to provide the study team with receipts, and study-related expenses will be reimbursed. Subjects will be provided with an information sheet (Appendix AA: Patient Reimbursement Info Sheet) describing the reimbursement process.

5.6 Adverse Reactions and Their Management

5.61 Reporting Adverse or Unanticipated Events

Potential adverse events (AE) for this project are expected to be all non-medical in nature. There is small risk of physical injury. Participants could experience discomfort while wearing the Fitbit Charge 2 on their wrist. There is also a chance participants could worsen repetitive use injuries (e.g., carpal tunnel syndrome) while using the smartphone app. Subjects may experience mild anxiety when answering survey questions about emotional issues or questions about coping challenges or difficulties related to discussing the subject matter. The PI will report unanticipated and serious adverse events to the IRB in a timely manner on an ongoing basis. For the purpose of this study a Serious Adverse Event (SAE) is defined as an event that, as a direct result of the study, causes serious harm to the subject (e.g., hospitalization).

5.62 Anticipated Reactions & Reaction Management

Should participants become exceedingly upset, disoriented or fatigued or need to attend to matters of personal care during the surveys, study staff will ask the subject if they would like to take a break or reschedule the survey for another time. In the event that participants experience distress while completing surveys, we will follow standard procedures used in our behavioral health intervention studies for counseling and referral. The PI will be notified immediately, and participants will be provided with the pager numbers for both the study PI and the study psychiatrist included in the consent form. Dr. Ilana Braun, a DFCI psychiatrist, has agreed to serve as a psychiatrist on the study. Dr. Braun will evaluate any participants who are distressed for risk of imminent danger and refer them to appropriate services if they are needed.

As noted in the study procedures, all clinical staff will be trained in the study protocol. A participants' clinical care team will be notified of every incoming call to the triage nurses, per standard practice, and her physician will be paged in the case of an emergency.

6.0 STATISTICAL ANALYSIS

6.1 Primary and Secondary Endpoints

Primary Endpoints: First Phase

1) To assess the feasibility and acceptability of the HOPE app and the two wearable accelerometers
2) To compare two wearable accelerometers (Fitbit Zip and Fitbit Charge 2) with respect to correlations with clinical outcomes (ECOG PS and patient-reported quality of life and physical health as measured by the PROMIS Global-10 items 2 and 3), for use in pilot RCT.

Secondary Endpoints: First Phase

1) To describe correlations between data collected from the HOPE app and the wearable accelerometers with additional clinical outcomes: PRO-CTCAE, CTCAE, and EQ-5D-5L.

Primary Endpoint: Second Phase

1) Health-related quality of life, comparing the patient-reported baseline and 6-month EuroQol EQ-5D.

Secondary Outcomes: Second Phase

1) Health care utilization (i.e. emergency room visits, hospitalizations, unplanned infusion appointments, and number of patient phone calls)
2) Correlation between patient and physician estimates of performance status
3) Additional clinical outcomes (e.g. anxiety and depression).
4) Correlation between data collected from the wearable and smartphone accelerometers
5) Predictive ability of wearable and smartphone accelerometers for patient's performance status and clinically significant events
6) Difference in correlation between data collected from the wearable and smartphone accelerometers, and difference in predictive ability of smartphone accelerometers for patient's performance status and clinically significant events, by whether patients are encouraged to wear their smartphones

6.2 Sample Size and Statistical Power or Precisions

A convenience sample of 10 patients will be enrolled to the first phase of the study. Due to the limited sample size, statistical analysis will be descriptive in nature.

100 patients will be enrolled to the second phase of this study, which will employ a 2x2 factorial design as depicted in the table below. Patients will be randomized 1:1:1:1 to one of the four arms.

Fitbit	App	Arm	Sample size
+	Active	1 (Fitbit + active app)	25
+	Passive	2 (Fitbit + passive app)	25
-	Active	3 (Active app)	25
-	Passive	4 (Passive app)	25
		Total	100

For the outcome of change in EQ-5D, we will use a one-sided type I error rate of 5% to conclude that an intervention is promising for further study. Based on prior literature,[22] the standard deviation of the change in EQ-5D at 6 months compared to baseline is approximately 14 points. With a total sample size of 100 patients (25 patients per arm), the table below summarizes the power to conclude that the either or both of the interventions are promising for further study based on a variety of effect sizes.

Difference in EQ-5D versus Usual Care			**Power to conclude that intervention is promising for further study**	
HOPE App	Wearable accelerometer	HOPE App + Wearable accelerometer	HOPE App	Wearable accelerometer
6	0	6	70%	--
7	0	7	80%	--
6	3	9	70%	28%
7	3	10	80%	28%
6	3	8	62%	23%
7	3	8	68%	17%

6.3 Intervention Allocation Plan

In the second phase, enrolled participants will be randomized to one of the four arms: 1) Fitbit + active app, 2) Fitbit + passive app, 3) Active app, 4) Passive app—using a 1:1:1:1 ratio. Enrolled participants will undergo a secondary randomization to being encouraged to use a smartphone, or not encouraged to use a smartphone. Randomization to the main study arms will occur using a computer-generated random allocation sequence with blocks of 8 in order to maintain balance between study arms over time. Study staff will generate group assignments in sequentially numbered and sealed opaque envelopes.

6.4 Analysis Plan

First phase:

Due to the limited sample size, statistical analysis will be descriptive in nature. Refinement of the HOPE App and selection of the wearable accelerometer to use in the second phase will be based on a descriptive assessment of feasibility, acceptability, and correlations with clinical outcomes.

Feasibility: We will record the proportion of eligible patients who enroll in the study and basic reasons for refusal [i.e. "too busy," "not interested," "other (specify)"]. Among those who enroll, we will plot the proportion who complete daily (quality of life, self-rated health, and PRO-CTCAE questions) and weekly (Promis PF 6b) surveys from the HOPE App over time, and the average steps per day obtained from each of the accelerometers. We will also descriptively summarize the proportion of clinicians complete the CTCAE and performance status data for enrolled patients at baseline and post-baseline.

Acceptability: Upon completion of the study, participants will be asked several questions, including: 1) "Participating in this study placed a substantial burden on me" and 2) "I wish I had not agreed to participate in this study." Responses to these items will be summarized descriptively.

Refinement of the HOPE App:
Participants will be asked about their experiences using the HOPE app, including: "Was the app helpful for managing your symptoms?" Participants will be asked about the frequency, format, and content of the app-based surveys, and whether there were symptoms that were missing from the app. Participants will also be asked open-ended questions, including: "What did you like about the app?" "What was most frustrating [about the HOPE app]?", "How could it [the HOPE app] have better met your needs?", and "Would you recommend this to a friend going through treatment? Why?" Responses to these items will be summarized descriptively.

Comparison between two wearable accelerometers:
Participants will also be asked several questions about their experience using the Fitbit, including: "Which Fitbit did you like better?" Response options will include: "Fitbit Zip (worn on your waistband)," Fitbit Charge 2 (worn on your wrist)," "No preference," and "Neither." Participants will be asked an open-ended question: "Why did you like the [FitbitZip/Fitbit Charge 2] better?" Participants will also be asked to what extent they agree with the following questions: "The Fitbit Charge 2 was easy to use" and "The Fitbit Zip was easy to use." We will also ask participants how many waking hours they wore each device daily (i.e. % waking hours), and how many times they forgot to wear the device or forgot to recharge it. Responses to these items will be summarized descriptively.

Correlations with clinical outcomes:
We will descriptively summarize correlations between data collected from the HOPE app (quality of life and physical function) and the wearable accelerometers (average daily steps) with clinical outcomes collected at baseline and post-baseline (i.e. performance status, quality of life, and symptoms assessment as obtained from the PRO-CTCAE and CTCAE).

Second phase:

In addition to descriptive analyses and estimating correlations between passive smartphone data and clinical outcomes, passive data may contain information that allows for the prediction of future clinically-relevant events, such as visits to the emergency department, urgent clinic encounter, or hospitalization. By testing for changes in activity, mobility, and social patterns over time as measured through smartphone use may be able to identify significant anomalies in patient behavior in the days prior to relapse. In a study in a cohort with schizophrenia, behavioral anomalies detected in the two weeks prior to clinical relapse occurred at a rate 71% higher than anomalies detected on other days.[92] The method is based on a modification of the Hotelling's T test to detect changes in the distribution of previous passively-measured activity. In our proposed study, this method might be used to query patients in real time to detect if an unscheduled clinical event might occur in the near future. Analyses will be repeated within secondary randomization arm to explore whether correlations and predictive ability of information from smartphone accelerometers are lower when participants are not encouraged to wear their smartphones.

For the primary analysis, the EQ-5D index scores will be calculated in each study arm at both baseline and 6 months and compared. The effect of the Fitbit on EQ-5D will be obtained by comparing the mean change in EQ-5D among all arms that consist of the Fitbit (i.e. arms 1 and 2) versus that obtained among all arms that do not consist of the Fitbit (i.e. arms 3 and 4). Similarly, the effect of the HOPE app on EQ-5D will be obtained by comparing the mean change in EQ-5D among all arms that consist of the HOPE app (i.e. arms 1 and 3) versus that obtained among all arms that do not consist of the HOPE app (i.e. arms 2 and 4). Additionally, pair-wise comparisons will be conducted of arms 2, 3, and 4 to arm 1 to examine which arms are driving or diluting any differences observed. Mean score changes from baseline will be compared using t tests and multivariable linear regression. The multivariable linear regression model will consist of change score as the dependent variable, and will adjust for baseline covariates (age, sex, cancer type, race, education, and literacy and numeracy). Additional analyses will use Fisher's exact test to compare the proportion of patients in each study arm who experience an improvement, no change, or a decrement in quality of life. This will be conducted both for any level of change from baseline and for a 6-point change from baseline (the threshold for a clinically meaningful difference). Similar analyses will be conducted for the secondary outcomes, including anxiety, depression, and number of patient phone calls, using the appropriate regression model (e.g. negative binomial regression may be used for the outcome of the number of patient phone calls).

For the health care utilization endpoints of unplanned infusion appointments, emergency room visits, and hospitalizations, cumulative incidence functions will be calculated with death treated as a competing event. Competing risk regressions will be used to model risk with and without adjustment for baseline covariates.

Agreement between patient-oncologist estimates of performance status will be estimated by Cohen's Kappa statistic, and differences in agreement between the study groups will be tested by bootstrapping.

6.5 Handling of Missing Data

For the primary quality-of-life analysis, we will exclude from our analyses any patients who do not complete any post-baseline EQ-5D questionnaires and carry forward the last post-baseline observation available for patients without 6-month data. If >10% of participants have missing data from the 6-month survey, we will perform sensitivity imputation analyses including: 1) no observations carried forward, 2) minimum observation values carried forward, 3) average observation values carried forward, and 4) last observation carried forward, but with an EQ-5D value of 0 if death occurred before 6 months.

7.0 REFERENCES

1. Di Maio M, Gallo C, Leighl NB, et al: Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 33:910-5, 2015
2. Fromme EK, Eilers KM, Mori M, et al: 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 22:3485-90, 2004
3. Montemurro F, Mittica G, Cagnazzo C, et al: Self-Evaluation of Adjuvant Chemotherapy-Related Adverse Effects by Patients With Breast Cancer. JAMA Oncol:1-8, 2015
4. Bennett AV, Reeve BB, Basch EM, et al: Evaluation of pedometry as a patient-centered outcome in patients undergoing hematopoietic cell transplant (HCT): a comparison of pedometry and patient reports of symptoms, health, and quality of life. Qual Life Res 25:535-46, 2016
5. Santana MJ, Feeny D, Johnson JA, et al: Assessing the use of health-related quality of life measures in the routine clinical care of lung-transplant patients. Qual Life Res 19:371-9, 2010
6. Detmar SB, Muller MJ, Schornagel JH, et al: Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA 288:3027-34, 2002
7. Velikova G, Booth L, Smith AB, et al: Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 22:714-24, 2004
8. Velikova G, Keding A, Harley C, et al: Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: secondary outcomes of a randomised controlled trial. Eur J Cancer 46:2381-8, 2010
9. Kotronoulas G, Kearney N, Maguire R, et al: 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 32:1480-501, 2014
10. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol, 2015
11. Denis F, C. L, Pourel N, et al: Overall survival in patients with lung cancer using a web-application-guided follow-up compared to standard modalities: Results of phase III randomized trial, J Clin Oncol 2016
12. Bakitas MA, Tosteson TD, Li Z, et al: Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial. J Clin Oncol 33:1438-45, 2015
13. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-42, 2010
14. Zimmermann C, Swami N, Krzyzanowska M, et al: Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 383:1721-30, 2014
15. Bakitas M, Lyons KD, Hegel MT, et al: Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 302:741-9, 2009
16. Schenker Y, Arnold R: The Next Era of Palliative Care. JAMA 314:1565-6, 2015
17. Basch E, Artz D, Dulko D, et al: Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 23:3552-61, 2005
18. Basch E, Jia X, Heller G, et al: Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 101:1624-32, 2009
19. Dueck AC, Mendoza TR, Mitchell SA, et al: Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 1:1051-9, 2015
20. Judson TJ, Bennett AV, Rogak LJ, et al: Feasibility of long-term patient self-reporting of toxicities from home via the Internet during routine chemotherapy. J Clin Oncol 31:2580-5, 2013

21. Girault A, Ferrua M, Lalloue B, et al: Internet-based technologies to improve cancer care coordination: current use and attitudes among cancer patients. Eur J Cancer 51:551-7, 2015
22. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016
23. Smith A PD: U.S. Smartphone Use in 2015, Pew Research Center
24. "The Smartphone Difference", Pew Research Center, 2015
25. Guillory J, Chang P, Henderson CR, Jr., et al: Piloting a Text Message-based Social Support Intervention for Patients With Chronic Pain: Establishing Feasibility and Preliminary Efficacy. Clin J Pain 31:548-56, 2015
26. Gustafson DH, McTavish FM, Chih MY, et al: A smartphone application to support recovery from alcoholism: a randomized clinical trial. JAMA Psychiatry 71:566-72, 2014
27. Torous J SP, Shanahan M, Lin C, Peck P, Keshavan M, Onnela JP: Utilizing a personal smartphone custom app to assess the Patient Health Questionnaire-9 (PHQ-9) depressive symptoms in patients with major depressive disorder. JMIR Mental Health 2:e8, 2015
28. Lester RT, Ritvo P, Mills EJ, et al: Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 376:1838-45, 2010
29. Chow CK, Redfern J, Hillis GS, et al: Effect of Lifestyle-Focused Text Messaging on Risk Factor Modification in Patients With Coronary Heart Disease: A Randomized Clinical Trial. JAMA 314:1255-63, 2015
30. Torous J, Staples P, Onnela JP: Realizing the potential of mobile mental health: new methods for new data in psychiatry. Curr Psychiatry Rep 17:602, 2015
31. Lowe SS, Danielson B, Beaumont C, et al: Associations between objectively measured physical activity and quality of life in cancer patients with brain metastases. J Pain Symptom Manage 48:322-32, 2014
32. Lowe SS, Danielson B, Beaumont C, et al: Correlates of objectively measured sedentary behavior in cancer patients with brain metastases: an application of the theory of planned behavior. Psychooncology 24:757-62, 2015
33. Maddocks M, Byrne A, Johnson CD, et al: Physical activity level as an outcome measure for use in cancer cachexia trials: a feasibility study. Support Care Cancer 18:1539-44, 2010
34. Maddocks M, Wilcock A: Exploring physical activity level in patients with thoracic cancer: implications for use as an outcome measure. Support Care Cancer 20:1113-6, 2012
35. Sorensen JB, Klee M, Palshof T, et al: Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 67:773-5, 1993
36. Hutchinson TA, Boyd NF, Feinstein AR, et al: Scientific problems in clinical scales, as demonstrated in the Karnofsky index of performance status. J Chronic Dis 32:661-6, 1979
37. Blagden SP, Charman SC, Sharples LD, et al: Performance status score: do patients and their oncologists agree? Br J Cancer 89:1022-7, 2003
38. Dajczman E, Kasymjanova G, Kreisman H, et al: Should patient-rated performance status affect treatment decisions in advanced lung cancer? J Thorac Oncol 3:1133-6, 2008
39. Ando M, Ando Y, Hasegawa Y, et al: Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. Br J Cancer 85:1634-9, 2001
40. Basch E, Wood WA, Schrag D, et al: Feasibility and clinical impact of sharing patient-reported symptom toxicities and performance status with clinical investigators during a phase 2 cancer treatment trial. Clin Trials, 2015
41. Dahele M, Skipworth RJ, Wall L, et al: Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage 33:676-85, 2007
42. Skipworth RJ, Stene GB, Dahele M, et al: Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr 30:812-21, 2011
43. Czajkowski SM, Powell LH, Adler N, et al: From ideas to efficacy: The ORBIT model for developing behavioral treatments for chronic diseases. Health Psychol 34:971-82, 2015

44. Basch EM, Thaler HT, Shi W, et al: Use of information resources by patients with cancer and their companions. Cancer 100:2476-83, 2004
45. EuroQol G: EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 16:199-208, 1990
46. Janssen MF, Pickard AS, Golicki D, et al: Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 22:1717-27, 2013
47. Kim SH, Kim HJ, Lee SI, et al: Comparing the psychometric properties of the EQ-5D-3L and EQ-5D-5L in cancer patients in Korea. Qual Life Res 21:1065-73, 2012
48. Sullivan PW, Ghushchyan V: Mapping the EQ-5D index from the SF-12: US general population preferences in a nationally representative sample. Med Decis Making 26:401-9, 2006
49. Pickard AS, Neary MP, Cella D: Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 5:70, 2007
50. Cella D, Riley W, Stone A, et al: The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 63:1179-94, 2010
51. Hays RD, Bjorner JB, Revicki DA, et al: Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 18:873-80, 2009
52. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-55, 1982
53. Basch E, Iasonos A, Barz A, et al: Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 25:5374-80, 2007
54. Lowe B, Kroenke K, Herzog W, et al: Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord 81:61-6, 2004
55. Thekkumpurath P, Walker J, Butcher I, et al: Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer 117:218-27, 2011
56. Johns SA, Kroenke K, Krebs EE, et al: Longitudinal comparison of three depression measures in adult cancer patients. J Pain Symptom Manage 45:71-82, 2013
57. Spitzer RL, Kroenke K, Williams JB: Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 282:1737-44, 1999
58. Spitzer RL, Kroenke K, Williams JB, et al: A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166:1092-7, 2006
59. Lowe B, Decker O, Muller S, et al: Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 46:266-74, 2008
60. Andersen BL, DeRubeis RJ, Berman BS, et al: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 32:1605-19, 2014
61. Wright AA, Mack JW, Kritek PA, et al: Influence of patients' preferences and treatment site on cancer patients' end-of-life care. Cancer 116:4656-63, 2010
62. Prigerson HG: Socialization to dying: social determinants of death acknowledgement and treatment among terminally ill geriatric patients. J Health Soc Behav 33:378-95, 1992
63. Wright AA, Zhang B, Ray A, et al: Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 300:1665-73, 2008
64. Fried TR, Bradley EH, Towle VR: Assessment of patient preferences: integrating treatments and outcomes. J Gerontol B Psychol Sci Soc Sci 57:S348-54, 2002
65. Chen JY, Tao ML, Tisnado D, et al: Impact of physician-patient discussions on patient satisfaction. Med Care 46:1157-62, 2008
66. Weeks JC, Catalano PJ, Cronin A, et al: Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 367:1616-25, 2012

67. Mack JW, Nilsson M, Balboni T, et al: Peace, Equanimity, and Acceptance in the Cancer Experience (PEACE): validation of a scale to assess acceptance and struggle with terminal illness. Cancer 112:2509-17, 2008

68. Lyons KD, Bakitas M, Hegel MT, et al: Reliability and validity of the Functional Assessment of Chronic Illness Therapy - Palliative care (FACIT-Pal) scale. J Pain Symptom Manage 37(1): 23-32, 2009

69. Wallace LS, Rogers ES, Roskos SE, et al: Brief report: screening items to identify patients with limited health literacy skills. J Gen Intern Med 21:874-7, 2006

70. Stagliano V, Wallace LS: Brief health literacy screening items predict newest vital sign scores. J Am Board Fam Med 26:558-65, 2013

71. Bakke E: A Model and Measure of Mobile Communication Competence. Human Communication Research 36:348-371, 2010

72. Stanton AL, Danoff-Burg S, Swarowski LA, et al: Randomized, controlled trial of written emotional expression and benefit finding in breast cancer patients. J Clin Oncol 20:4160-4168, 2002

73. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373-83, 1987

74. Takacs J, Pollock CL, Guenther JR, et al: Validation of the Fitbit One activity monitor device during treadmill walking. J Sci Med Sport 17:496-500, 2014

75. Lee JM, Kim Y, Welk GJ: Validity of consumer-based physical activity monitors. Med Sci Sports Exerc 46:1840-8, 2014

76. Tully MA, McBride C, Heron L, et al: The validation of Fibit Zip physical activity monitor as a measure of free-living physical activity. BMC Res Notes 7:952, 2014

77. Adam Noah J, Spierer DK, Gu J, et al: Comparison of steps and energy expenditure assessment in adults of Fitbit Tracker and Ultra to the Actical and indirect calorimetry. J Med Eng Technol 37:456-62, 2013

78. Kooiman TJ, Dontje ML, Sprenger SR, et al: Reliability and validity of ten consumer activity trackers. BMC Sports Sci Med Rehabil 7:24, 2015

79. Kurti AN, Dallery J: Internet-based contingency management increases walking in sedentary adults. J Appl Behav Anal 46:568-81, 2013

80. Evenson KR, Goto MM, Furberg RD: Systematic review of the validity and reliability of consumer-wearable activity trackers. Int J Behav Nutr Phys Act 12:159, 2015

81. Wallen MP, Gomersall SR, Keating SE, et al: Accuracy of Heart Rate Watches: Implications for Weight Management. PLoS One 11:e0154420, 2016

82. de Zambotti M, Baker FC, Willoughby AR, et al: Measures of sleep and cardiac functioning during sleep using a multi-sensory commercially-available wristband in adolescents. Physiol Behav 158:143-9, 2016

83. Atallah L, Lo B, King R, et al: Sensor positioning for activity recognition using wearable accelerometers. IEEE Trans Biomed Circuits Syst 5:320-9, 2011

84. Cadmus-Bertram L, Marcus BH, Patterson RE, et al: Use of the Fitbit to Measure Adherence to a Physical Activity Intervention Among Overweight or Obese, Postmenopausal Women: Self-Monitoring Trajectory During 16 Weeks. JMIR Mhealth Uhealth 3:e96, 2015

85. Case MA, Burwick HA, Volpp KG, et al: Accuracy of smartphone applications and wearable devices for tracking physical activity data. JAMA 313:625-6, 2015

86. Cadmus-Bertram LA, Marcus BH, Patterson RE, et al: Randomized Trial of a Fitbit-Based Physical Activity Intervention for Women. Am J Prev Med 49:414-8, 2015

87. Morgan NP, Graves KD, Poggi EA, et al: Implementing an expressive writing study in a cancer clinic. The Oncologist 13:196-204, 2008

88. Smith S, Anderson-Hanley C, Langrock A, et al: The effects of journaling for women with newly diagnosed breast cancer. Psycho-Oncology 14:1075-1082, 2005

89. Lepore DJ, Revenson TA, Roberts KJ, et al: Randomised controlled trial of expressive writing and quality of life in men and women treated for colon or rectal cancer. Psychology & Health, 30(3):284-300, 2015

90. Lacetti M: Expressive Writing in Women with Advanced Breast Cancer. Oncology Nursing Forum 34(5), 2007

91. Carver CS. You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med. 1997;4(1):92-100. doi:10.1207/s15327558ijbm0401_6.

92. Barnett I, Torous J, Staples P, Sandoval L. Relapse Prediction in Schizophrenia through Digital Phenotyping: A Pilot Study. Journal of the American Medical Informatics Association. Submitted.

8.0 APPENDICES

Recruitment/Enrollment:

Appendix A: Opt-out card
Appendix B: Registration Form
Appendix AA: Reimbursement Sheet

Instruments:

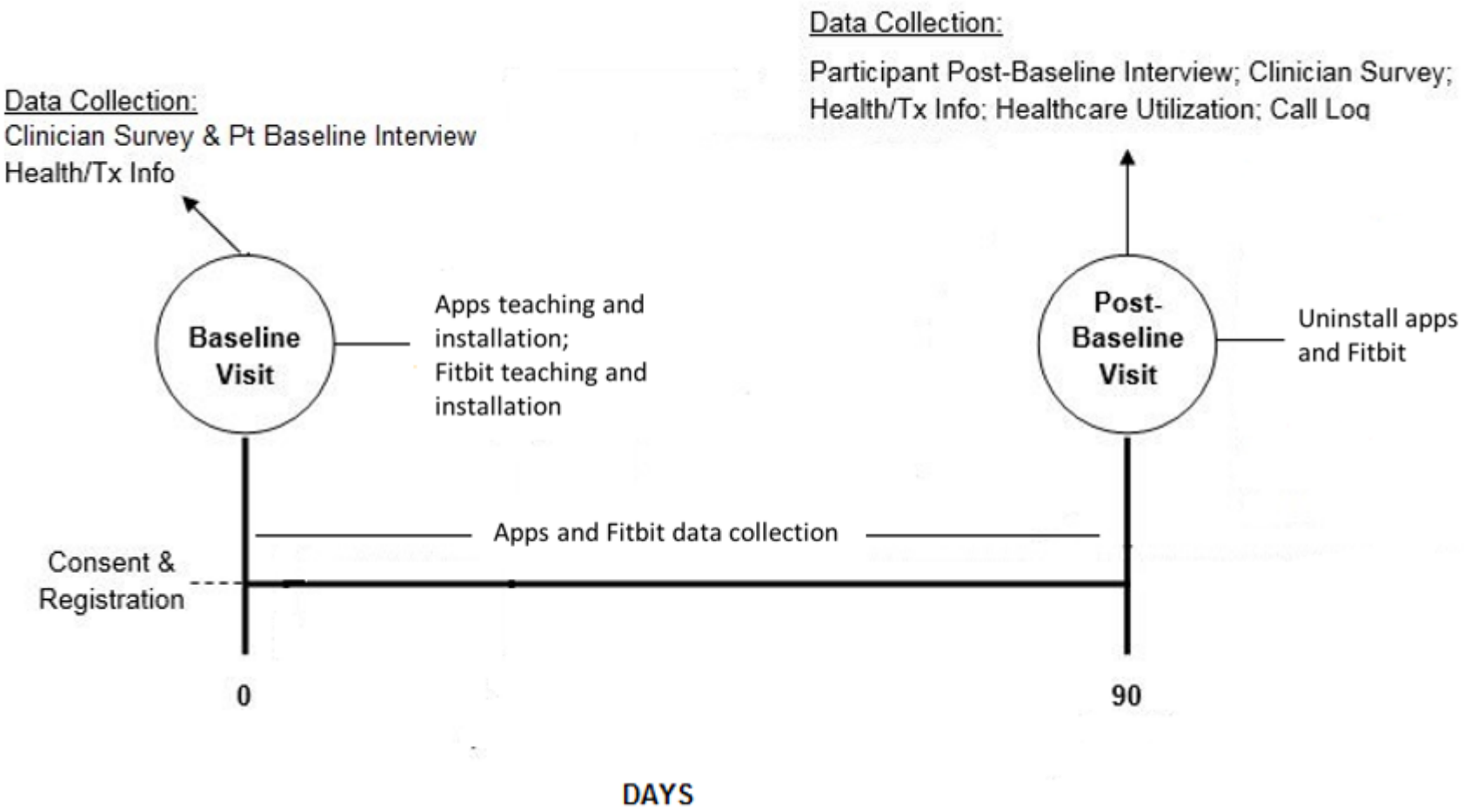
Appendix C: Participant Baseline Survey
Appendix D: Participant Post-Baseline Survey
Appendix E: Clinician Survey
Appendix F: Symptom Survey
Appendix G: Health/Tx Information
Appendix H: Health Care Utilization
Appendix I: Call Log
Appendix J: Debriefing Interviews
Appendix Z: Medical Resource Utilization Form

Interventions:

Appendix K: HOPE App Features and Screenshots
Appendix L: HOPE App Data Privacy and Security
Appendix M: Symptom Management Content
Appendix N: HOPE App Required Reading & Discussion
Appendix O: HOPE App Participant Guide for Active App
Appendix P: Summary Sheet for Participants
Appendix Q: Fitbit Participant Guide
Appendix R: Summary Sheet for Participants, Fitbit + passive app
Appendix S: Summary Sheet for Participants, Active app
Appendix T: Summary Sheet for Participants, Fitbit + active app
Appendix U: Common Fitbit problems
Appendix V: Sample Summary Sheet
Appendix W: HOPE App Participant Guide for Passive App
Appendix X: Summary Sheet for Participants, Passive App
Appendix Y: Encouraged to Wear Smartphone Reminder Sheet

Part 2
The SMART Study

SECTION 1: Study Schema for SMART (n=30)



SECTION 2: Body of Protocol

TABLE OF CONTENTS

1.0 INTRODUCTION, BACKGROUND AND RATIONALE

The goal of chemotherapy is to reduce symptoms and extend survival. Yet, oncologists' methods of monitoring patients' symptoms are underdeveloped. Studies show that clinicians consistently miss more than half of cancer patients' symptoms, even in clinical trials that mandate collection of treatment toxicities.[1,3] Similarly, oncologists' estimates of patients' performance statuses are highly subjective, yet key determinants of patients' eligibility for clinical trials, chemotherapy, and hospice. Oncologists' performance status assessments are only moderately correlated with one another[4,5] and are even less reliable when compared with patients' estimates.[6-8] This may be because clinicians see patients at fixed time points that are frequently tied to chemotherapy infusions, when patients have often already recovered from their last treatment. The moments between visits—when patients are at the highest likelihood of experiencing treatment toxicities—are far more likely to contain more meaningful data about patients' symptoms and activity levels.

Integration of patient-reported outcomes (PROs) into clinical practice is an increasingly promising strategy for improving patients' symptoms, communication, and clinical outcomes.[9,10] Basch et al. recently demonstrated that for patients with metastatic cancers, the use of a web-based system to assess PROs, combined with automated clinical alerts, resulted in better health-related quality of life, fewer emergency room visits and hospitalizations, and superior quality-adjusted survival, compared with usual care.[10] However, this study and others have predominantly assessed patients during clinic visits.[11] A key limitation to this approach is that it relies upon a patient's retrospective recall of events. Our research will be among the first to produce *real time* and *real world* assessments of cancer patients' symptoms and activity levels within their daily lives.

Smartphones offer an accessible, low-cost method for conducting *real time* and *real world* assessments of patients' symptoms and activity levels. A study conducted by members of our team demonstrated that patients with major depressive disorder used a smartphone app to answer questions from the Patient Health Questionnaire-9 (PHQ-9) 3 times per day over a 30-day period with >75% adherence.[12] Patients' scores were strongly correlated with standard paper-based surveys, but 3 points higher on average (reflecting more distress), and patients reported higher rates of suicidal ideation. We subsequently adapted this platform to assess symptoms using the PRO-CTCAE; risk-stratify patient responses; provide tailored feedback to patients with low-risk symptoms; and notify patients and clinicians of high-risk symptoms.[13] Preliminary data from a pilot in patients with gynecologic cancers at Dana-Farber Cancer Institute suggests that patients are able to use the app, have favorable impressions of it, and high adherence rates. Moreover, we have detected several clinically significant symptoms (e.g. severe vomiting, abdominal pain) which were not captured in routine clinical practice, and prevented emergency department visits by addressing them real-time.[14] Smartphones offer new strategies for assessing patients' symptoms, identifying toxicities, and intervening to reduce suffering.

Additionally, smartphones have the functionality to monitor social and behavioral markers of health and illness remotely using passively collected data (without patient involvement) to detect temporal changes and behavioral anomalies that can indicate the onset of clinically significant symptoms. Recently, a study conducted by Barnett and Onnela demonstrated the use of a smartphone platform, Beiwe, to detect relapses in patients with schizophrenia by identifying anomalies in their pre-relapse behaviors, including changes in their mobility and phone use patterns. This approach did not require active patient participation or the introduction of new technologies. Data were collected from participants' personal smartphones, making these devices an ideal and scalable technology for long-term remote monitoring with minimal participant burden.

Like smartphones, wearable accelerometers offer another novel means for collecting real world data to objectively measure patients' performance statuses. Patients' retrospective reports of activity levels are often inaccurate or imprecise. Without accurate information, oncologists may have difficulty objectively assessing patients' performance statuses, and may underestimate patients' symptom burdens and chemotherapy-related toxicities. Indeed, oncologist estimates of patients' performance statuses are only moderately correlated with

one another[4,5] and weakly correlated with patient estimates,[6-8] but improve when clinicians and patients participate in "shared" reporting of patients' toxicities and performance statuses.[15]

Wearable accelerometers are devices that track users' energy expenditures, the amount and intensity of physical activity, and sedentary behavior. They offer cost-effective, user-friendly, and objective measurements of patients' free living patterns. A few studies have piloted wearable accelerometers in adult cancer patients undergoing stem cell transplants (HCT) or treatment for colorectal, gastrointestinal, breast, and lung cancers.[16-19] Results from one study of adult patients undergoing HCT who wore accelerometers over an 8 week period found that patients' reports of severe symptoms, impaired physical health, and restrictions in activities of daily living were associated with statistically significant decrements in objectively measured steps, suggesting that this may be an independent, quantitative measure of quality of life and patient performance status.[16] In this study of 32 patients undergoing HCT over a 4-week period patients' steps were significantly associated with an increased symptom burden.[16] Similar results were observed in a population of patients receiving concurrent chemoradiation.[20] We expect that symptoms are likely to impact the amount of walking that patients can do and will therefore provide an independent measure of both patients' performance status and symptom burden.

The overall goals of this study are to test the combination of two smartphone research platforms, the SMART app and the Beiwe app, and a wearable accelerometer for use in NCI Community Oncology Research Program (NCORP) sites to improve cancer patients' quality of life and symptom management. The SMART Study (Symptom Management and Reporting Toxicities) has a single-arm research design and aims to assess feasibility, acceptability and perceived efficacy of a wearable accelerometer and two smartphone apps in 30 patients receiving chemotherapy to treat recurrent gynecologic cancers. The SMART intervention refers to the combination of both smartphone apps (SMART app and Beiwe app) and the accelerometer (Fitbit). The SMART app is the technology that is actively collecting symptom reporting information from patients (e.g. patients are receiving surveys, recording their symptoms daily, and receiving tailored symptom management materials on their phone in response). The Beiwe app is the technology involved in the passive data collection of participants' symptoms (GPS and accelerometer data) without their involvement.

2.0 OBJECTIVES

2.1 Primary Objectives

To conduct a single-arm study to assess feasibility and acceptability of two smartphone apps and a wearable accelerometer in 30 patients with gynecologic cancers receiving chemotherapy.

- Feasibility will be defined as: 1) ≥50% approach to enroll rate, and 2) ≥50% 3-month adherence rates to both smartphone apps and the wearable accelerometer.
- Acceptability will be defined as: ≥60% of study participants would recommend the intervention to other patients; and <30% of patients rate the study as burdensome or wish they had not participated.

2.2 Secondary Objectives:

Assess the perceived efficacy of the smartphone apps and wearable accelerometer and estimate outcome parameters for this population

- Perceived efficacy will be measured by qualitative analysis: We will conduct debriefing interviews with a subset of participants and clinicians to obtain information about the acceptability of the intervention and recommendations for any modifications to improve any aspects of recruitment, enrollment, education, the timing of study assessments, graphical displays of information, fitness tracker use, and the apps that could be improved.
- Outcome parameters will be estimated by quantitative analysis: We will descriptively summarize the distribution of toxicities and clinical outcomes at baseline and at 3-month follow-up.

3.0 RESEARCH SUBJECT SELECTION

3.1 Eligibility Criteria

- Women ≥18 years of age who plan to receive chemotherapy to treat recurrent, incurable gynecologic cancer (i.e., ovarian, fallopian, primary peritoneal, uterine, or cervical cancer) that has recurred despite ≥1 prior treatment.
- Own a smart phone (Android or iOS).
- Capable of downloading and running the study apps.
- Can read and provide informed consent in English.
- Does not have cognitive or visual impairments that would preclude use of the apps.

3.2 Exclusion Criteria

- Patients will be ineligible if they are participating in an investigational drug treatment trial that requires structured symptom or toxicity reporting at the time of enrollment.
- Patients with severe cognitive impairments or who appear too weak, emotionally distraught, agitated or ill to participate, as judged by either the research study staff or an oncology provider, will be excluded.
- Patients who are unable to provide informed consent in English will be excluded because the smartphone apps are only available in English at this time.
- Children and young adults up to age 17 will be excluded because the diagnosis of metastatic gynecologic cancers in this age group is rare and the proposed instruments are not designed for people of those ages.
- Patients with a life expectancy of ≤3 months, as determined by their oncology providers, will be excluded since they cannot participate in all of the required data collection.

4.0 RESEARCH SUBJECT ENTRY

4.1 Subject Recruitment and Enrollment

We will enroll patients from community oncology sites. Study staff, oncology providers, and clinic staff will identify patients who may be eligible for the study. Prior to initiating recruitment at each site, we will use a rigorous, stakeholder-driven process[21] to ensure that the apps and fitness tracker can be integrated into practice without disrupting the workflow or causing patient distress. For example, for a similar study using the adapted smartphone app and wearable accelerometers in women with gynecologic cancers at DFCI, our recruitment protocol includes: 1) reviewing clinicians' weekly schedules to identify potentially eligible patients for study enrollment, 2) contacting clinicians for permission to approach potentially eligible patients, and 3) introducing the study to the patient at the next clinic visit (e.g., describing the study, reviewing the consent form, answering questions, and obtaining written informed consent) before we enroll each patient. While this protocol has been successful at DFCI, we recognize that each clinical practice setting is unique and will work with practices to develop site-specific study recruitment and enrollment protocols.

4.11 Screening & Recruitment

Prior to obtaining informed consent, study staff will determine whether patients are eligible for the study. Study staff will identify patients with recurrent gynecologic cancers that have progressed through one or more treatments and who are planning to receive chemotherapy. Site-specific procedures will be developed to identify eligible patients, which may involve review of medical records and/or discussion with a patient's oncology providers. A HIPAA waiver requesting permission to review the PHI of potentially

eligible patients has been submitted to justify this process. If a patient's oncology provider deems the patient ineligible or too distressed to participate in a clinical study at this time, the patient will not be approached for inclusion. PHI obtained in the context of study recruitment will not be shared with anyone outside the study team and patients' oncology providers. For all enrolled participants, sites will document confirmation of participant eligibility by their providers.

4.12 Informed Consent

If a patient agrees to learn more about the study, study staff will describe the study, review the consent form, answer any questions, and provide contact information for the study team. The staff member will encourage patients to take their time in deciding whether they want to participate in the study or not.

If a patient is interested in participating, she will enter the informed consent process, which will include explaining how and why the current research study is being conducted, the study risks and benefits, the potential time commitment involved, and the option to give permission to be contacted for future research studies. The patient will learn what type of information will be collected from the smartphone applications and accelerometer and how these data are monitored. The staff member will reiterate that the data collected are not a part of the patient's standard treatment and will underscore the importance placed upon maintaining patient confidentiality and a patient's rights while involved in the study, including the right to withdraw participation at any time for any reason during the study because participation is completely voluntary.

The informed consent form will contain a section dedicated to explaining what constitutes PHI and how this information will be protected as confidential per HIPAA guidelines. The consent form will also provide contact information for both the Principal Investigator (PI) as well as the Office for the Protection of Research Subjects (or analogous body at local sites). All informed consent processes will adhere to the policies set forth by the Institutional Review Board. Signed informed consent forms will be stored in locked file cabinets to maintain the privacy of all study participants.

If a patient is unsure if she would like to participate in the study, she will be offered the consent form to review and the contact information of study staff. If the patient does not contact staff after a few days and further contact is appropriate, study staff will contact the patient. If the patient decides to participate, a staff member will engage in the informed consent process with the patient. If a patient is not interested, the staff member will thank her for considering, and reassure the patient that the process will have no impact on her clinical care. No further interactions will occur with patients who either decline or prove ineligible for the study.

4.2 Subject Registration

After informed consent is obtained, participants will be assigned a unique study ID and registered to the study in RedCap. Participants will be retrospectively registered in OnCore, the Clinical Trial Management System for Dana-Farber in a de-centralized fashion. Registrations may occur up to 30 days after consent is signed per REGIST-101.

5.0 STUDY DESIGN AND METHODS

5.1 Design/Study Type

In a single-arm study of patients at community oncology sites in the United States, we will employ convenience sampling from 30 patients who meet inclusion criteria. Our analyses involve estimations of feasibility, acceptability, and preliminary efficacy. In addition, we will assess safety outcomes, toxicity scale scores,

missing data, and patient/physician feedback. We will not conduct formal hypothesis testing in this small sample.

5.2 Selection of Instruments

5.21 Interviews and Surveys

The following measures will be used in the study interviews and surveys, including the *Participant Baseline Interview* (Appendix 14), *Participant Post-Baseline Interview* (Appendix 15), and *SMART App Surveys* (Appendix 16). Table 1 outlines their distribution across the study instruments.

5.21a Global Health Status: EQ-5D-5L

The EQ-5D is a standardized measurement of health status that has been used in a wide range of health conditions and treatments, including cancer patient populations.[23] The EQ-5D-5L is the most recent 5-level version that has proven validity and reliability in a range of patient groups with chronic diseases[24] and cancer.[25] It is a 5-item questionnaire (measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of perceived problems: 1) no problems, 2) slight problems, 3) moderate problems 4) severe problems, and 5) extreme problems. Patients check the statement level that best describes their current health status in each dimension, which are then scored to generate a patient's unique health state. In the EQ-VAS, patients report a single index value of how good or bad their current health state is on a visual scale that ranges from worst imaginable at zero to best imaginable at one hundred. The EQ-5D-5L can be administered with little to no guidance and takes only a few minutes to complete. Upon scoring, the EQ-5D produces a composite score between 0-1 (multiplied by 100 to generate a number between 0-100), which represents general health status, normalized for the US population.[26] Lower scores represent worse quality of life, and a change of ≥6 is clinically significant in US cancer populations.[27]

5.21b PROMIS Global-10 and PROMIS Physical Function short form 6b

The PROMIS Global-10 is a brief measure of patient health status that is not disease specific.[28,29] It consists of 10 questions; e.g. "In general, how would you rate your physical health?" Items are scored on a Likert scale of 1-5, where higher scores indicate better health, except for pain which is measured on a 10-point scale. Standardized T-scores (range 0-100) are calculated for the global physical and mental health scales, and higher scores indicate better health. The full scale takes approximately 2-3 minutes to complete and will be used in the baseline and post-baseline surveys, and in the SMART app.

The PROMIS Physical function (PF) 6b is a brief, 6-item measure used to characterize patients' overall health, level of physical disability, and general well-being. The PROMIS PF 6b has been validated in 4,840 cancer patients across a range of ages, racial/ethnicity groups, stages and cancer types, and normalized for the US population. It has high reliability, minimal floor effects, and can precisely measure meaningful differences in functional status, disease burden, and comorbidities. The full scale takes approximately 1-2 minutes to complete and will be used in the baseline and post-baseline surveys, and in the SMART app.

5.21c Performance Status: ECOG PS

The Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) assessment is a standard measurement that oncologists often use to assess a patient's current functional level and eligibility for clinical trials. The scale ranges from 0 to 5 and the criteria for each grade is as follows: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically

strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; 3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4 = Completely disabled; cannot carry on any self-care; totally confined to bed or chair; 5 = Dead.[30]

The ECOG PS will allow clinicians and participants to provide a standard evaluation of the participant's performance status over time and with minimal burden. Participants will use the patient self-report version that has been used successfully in a study with cancer patients. We expect that it will take 1-2 minutes to answer the question.[31]

5.21d Depression: modified PHQ-9

The Patient Health Questionnaire-9 (PHQ-9) is a validated self-report measure that assesses nine depressive symptoms using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for major depressive disorder. It is used to screen, diagnose, and monitor depressive symptoms[32] and has been administered/demonstrated validity in cancer patients,[33,34] as well as smartphone apps.[12] Respondents report if each symptom has bothered them "not at all," "several days," "more than half the days," or "nearly every day" during the previous two weeks.[35] We will not include question 9, which assesses suicidal ideation, since access to 24-hour psychiatry services may not be available at all sites. We expect that it will take participants no more than 3-5 minutes to complete the 8 questions.

5.21e Symptoms Assessment: PRO-CTCAE

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-centered, standardized self-report measure that enables patients to report symptoms and AEs.[10,11,36,37] The PRO-CTCAE has demonstrated validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment.[37] Ten PRO-CTCAE items that are salient to gynecologic cancers will be collected, including: abdominal pain, nausea, vomiting, constipation, diarrhea, peripheral neuropathy, anxiety, depression, dizziness and fatigue.

The PRO-CTCAE items use conditional branching for AEs that contain multiple attributes. For example, if a participant reports a symptom, she is asked to quantify the severity and the extent to which the symptom interfered with her daily activities; if she does not report a symptom, these items are skipped. We anticipate that participants will complete this measure in about 3-5 minutes at baseline and the end of the study. Patients will also report their symptoms daily through the SMART app.

5.21f Anxiety: GAD-7

The Generalized Anxiety Disorder 7-Item (GAD-7) is a reliable and validated self-report measure that assesses GAD. Respondents rate how often they have been bothered by 7 anxiety symptoms over the past two weeks using the following scale: 0 = Not at all; 1 = Several Days; 2 = Over half the days; and 3 = Nearly every day. Respondents also answer a question to assess the duration of their anxiety symptoms. Responses are tallied and the total score indicates the presence and severity of GAD.[38]

The measure has since been validated in the general population[39] and was the recommended evaluative measure for anxiety in adult cancer patients in the 2014 American Society of Clinical Oncology (ASCO) Guideline Adaptation.[40] We anticipate that it will take participants approximately 3-5 minutes to complete.

5.21g Overall Quality of Life and Physical Health: FACIT-PAL

Patients' quality of life (QoL) will be assessed with Functional Assessment of Chronic Illness Therapy – Palliative Care, which has demonstrated internal consistency, reliability and validity.[41] The measure is divided into four primary QoL domains: physical well-being (7-items), social/family well-being (7-items), emotional well-being (6-items), and functional well-being (7-items). It also includes 12 additional items that are specific to palliative care priorities for patients with chronic illnesses such as cancer. Participants will rate each symptom over the past 7 days as: 0) Not at all; 1) A little bit; 2) Somewhat, 3) Quite a bit, and 4) Very much. Subscales can be analyzed separately or aggregated to produce a total score. Patients will complete this at baseline and the end of the study. Through the SMART app, patients will also answer a brief weekly survey, Functional Assessment of Cancer Therapy-General (FACT-G7), which serves as a rapid assessment of patients' top-rated symptoms and concerns regarding cancer treatment. This measure allows physicians to quickly identify and address a broad range of issues that may affect a patient's quality of life.

5.21h Literacy Measures: Health Literacy and Numeracy & Mobile Communication Competence

Health literacy[42] and numeracy and mobile communication competence[43] will be collected for all participants at baseline. The "comfort with technology" and "mobile preference" subscales of the Mobile Communication Competence scale will be used because they assess factors directly impacting patients in our study, who will be asked to acclimate to and consistently use an accelerometer and/or smartphone apps. The mobile communication preference and comfort with technology subscales individually demonstrated internal reliability, consistency and validity. We estimate that it will take participants approximately 5 minutes to complete all of the literacy measures.

5.21i Demographic Information

Basic demographic information will be collected for all participants, including: age, marital status, race/ethnicity, education, household structure, income, and employment. The questions will only take a few minutes to complete.

5.21j Smartphone Usage Questions

Data on smartphone-specific usage habits will be collected for all participants. Participants will be asked a total of four questions: average daily time spent using smartphone, purpose of using smartphone, comfort using smartphone apps, and frequency of using smartphone apps. We estimate that it will take participants approximately 2 minutes to complete these questions.

5.21k Brief COPE

The Brief COPE is a 28-item measure developed to assess a broad range of coping responses.[46] The Brief COPE has been validated in several populations including breast cancer patients and community samples.[46] Subscales of the Brief COPE include use of emotional support, religion, and self-distraction, and individual subscales can be used independently. We will use the denial, behavioral disengagement, self-distraction, active coping, use of emotional support, use of instrumental support, positive reframing, planning, acceptance, and religion subscales of the Brief COPE. The Brief COPE will be administered to patients during the participant baseline interview

Table 1. Distribution of measures during Baseline and Post-Baseline Interviews.

		Baseline Interview	Post-baseline Interview	SMART App Surveys
MEASURE	PRO-CTCAE	□	□	□
	PROMIS Global-10 and Physical Function 6b	□	□	□
	ECOG PS	□	□	
	PHQ-9	□	□	
	GAD-7	□	□	
	EQ-5D-5L	□	□	
	FACIT-PAL	□	□	
	Brief COPE	□		
	Health Literacy & Numeracy	□		
	Mobile Communication Competence	□		
	Smartphone Usage Questions	□		
	Demographic Info	□		
	Healthcare Utilization		□	

5.22 Medical Chart Abstractions and Patient-Reported Medical Resource Utilization

5.22a Health/Treatment Information

Participants' medical charts will be reviewed to abstract health and treatment related information, including disease site, comorbid health conditions,[47] number of prior chemotherapy regimens, and time since diagnosis. Data will be recorded in the *Health/Tx Info* form (Appendix 17).

5.22b Health Care Utilization

At baseline participants will be given a patient diary to record all health care utilization that occurs during the study period, including hospitalizations, admissions to an intensive care unit, emergency room and urgent care visits, and oncology visits. This form was developed by the NRG Cancer Care Delivery Research Group because of recognition that participants often receive care outside of NRG sites that cannot be captured by the medical record. Clinical research coordinators will be asked to verify medical care that happened within a site-affiliated medical center. Participants' medical charts will be reviewed to abstract health care utilization data during enrollment, including chemotherapy regimen and treatments, palliative care visits, emergency department visits, hospitalizations, and hospice referrals. If a participant dies while enrolled in the study, the date of death will also be recorded. Data will be recorded in the Health Care Utilization form (Appendix 18). Additionally, participants will be asked about whether they (or their informal caregiver) needed to take time off from work, how far they traveled for treatment, and for a rough estimate of their out-of-pocket expenditures to capture some of the burden associated with cancer care.

5.22c Call Log

If the data is available, study staff will abstract information about phone calls to their providers during a participant's enrollment and record data in the *Call Log* (Appendix 19). Data collected for each call will include: date/time, incoming/outgoing, left message, duration in minutes, reason for the call, symptoms documented, and the outcome.

5.23 Debriefing Interviews

Debriefing Interviews will be conducted with a purposively sampled subset of participants, approximately 15 across all sites. The purpose of these interviews is to obtain information about the acceptability of the interventions and recommendations for modifications to improve any aspect of recruitment, enrollment, education, timing of study assessments, the graphical display of information, and the smartphone apps. The interview guide can be found in Appendix 20. In accordance with qualitative interviewing procedures, additional themes and topics that arise over the course of the study may be explored further in the debriefing interview, in addition to the list of questions in the interview guide. Study staff will aim to administer debriefing interviews to the first few patients enrolled at each site and an additional purposively sampled subset of patients; debriefing interviews will be conducted for approximately 15 patients total. Study staff will also solicit debriefing feedback from clinicians who are serving as co-investigators on the study and site research staff who are managing the clinician dashboard. If site policy permits, participating co-investigators and site staff will receive gift cards in appreciation of the time they have dedicated to study debriefing. The feedback provided by co-investigators and site staff will be used to further refine integration of the study into clinical workflow and improve the effectiveness of the study.

Additionally, debriefing interviews will be audiotaped in order to ensure that the interviewer adequately captures all feedback from patients, co-investigators, and site staff. The consent forms for the study include information that the debriefing interview will be audiotaped, and we will verbally request permission from patients, co-investigators, and site staff to audiotape the debriefing interview before beginning the interview. Verbal permission will be documented on RedCap. We will not administer a debriefing interview to any person who does not consent to being audiotaped during the debriefing interview. All audio recordings of study sessions will be stored in secure, restricted-access locations. Recordings will be tied only to a study ID number, and the only documents linking the patient's study ID to identifiable information are in a restricted-access file stored securely on restricted-access folders. Audiotapes of debriefing interviews will be transcribed for further analysis using a DFCI-approved, HIPAA-compliant transcription vendor or locally at Dana-Farber. All patient identifiable information will be removed when the audio recordings are transcribed. Audio recordings of debriefing interviews will be destroyed when analyses are complete.

5.3 Description of Interventions

The SMART intervention is a mobile health intervention that consists of two smartphone apps, and a wearable accelerometer. For this study, the smartphone apps are named the "SMART app" and "Beiwe app" and the accelerometer is the Fitbit Charge 3.

5.31 Smartphone apps

The SMART study intervention is based on two iOS and Android smartphone applications, the SMART app and Beiwe app, which run on participants' personal smartphones and collect information about their health and behaviors. The SMART app employs "active" data which require direct participant

involvement—for example survey responses. The Beiwe app collects "passive" data, which are generated without any direct participant involvement—for example, GPS or accelerometry.

The "Beiwe," app was conceived and designed by one of the co-investigators, Dr. Jukka-Pekka Onnela, at the Harvard T.H. Chan School of Public Health. Zagaran, Inc., located in Cambridge, Massachusetts, built the software. One of the advantages of the Beiwe app is that it protects identifying data through hashing, and all data are encrypted while on the device, in transit, and stored on the server. Once collected by the phone, raw data are encrypted and securely transmitted to an instance of Amazon S3 for storage and later retrieval for analysis.

In a prior pilot study, Dr. Onnela tested the app in 13 patients with major depressive disorder. Participants installed the app on their personal smartphones and completed a self-report survey of PHQ-9 items 3 times per day with >75% adherence to the app over a 30-day period.[12] Participants scores were strongly correlated with paper-based surveys administered in clinic (Pearson linear correlation coefficient 0.84) but were 3.0 points higher on average (i.e. indicating more distress), and participants were much more likely to report significant suicidal ideation.

Since this publication, Dr. Onnela's lab has developed a more sophisticated system that features a web-based research study portal, a customizable Android and iOS smartphone app, Amazon Web Services S3 database, and data modeling and analysis tools. The app collects many different types of sensor data and administers surveys. There are currently several IRB approved protocols across local centers that are utilizing the Beiwe application in research, including Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Harvard University (Faculty of Arts and Sciences), McLean Hospital, and Massachusetts General Hospital. Several studies have begun enrolling patients or healthy controls, and the user experience has been overwhelmingly positive. In addition, there are no signs that adherence is condition-specific to date.

We subsequently adapted this platform to assess symptoms using the PRO-CTCAE; risk-stratify patient responses; provide tailored feedback to patients with low-risk symptoms; and notify patients and clinicians of high-risk symptoms. Preliminary data from a pilot in patients with gynecologic cancers at Dana-Farber Cancer Institute suggests that patients are able to use the app, have favorable impressions of it, and high adherence rates. Moreover, using this app we detected several clinically significant symptoms (e.g. severe vomiting, abdominal pain) which were not captured in routine clinical practice, and prevented emergency department visits by addressing them real-time.[14]

The Beiwe platform has the functionality to evaluate patients' health behaviors and activities by collecting either active or passive data, or both concurrently. Through previous research, we discovered the research platform did not have a clinician-facing interface to enable tracking of individual symptoms in real-time, or a clinician dashboard to enable study staff to monitor a population of patients simultaneously. This meant that study participants' symptoms could be downloaded once daily into a pdf for the full population, and this was format was infeasible for a multi-site study. Moreover, patients reported that the surveys were "not engaging," and Beiwe would not be easily adapted to a more engaging format.

Based upon these experiences, the study team at Dana-Farber concluded that there was a significant need to develop a better patient- and clinician facing interface for engagement and population management before launching a multi-site trial. As a result, the decision was made to seek out a different technology platform that could meet these needs. Once an appropriate platform was identified, the decision was made to turn off the "active" data collection features of the Beiwe app, with a plan to continue using Beiwe for "passive" data collection. We then partnered with a different company to design a new smartphone app on a different platform for active data collection. For the SMART app redesign, we partnered with RMDY Health, an established commercial digital health provider that creates mobile health

and web programs, including interventions for medication management, weight loss, prevention, adherence, and lifestyle modification programs.

In collaboration with RMDY, Dana-Farber study staff were able to design a custom "white-label" digital health platform catered specifically to the patient population involved in this research study. The RMDY platform is comprised of three main components: 1) an app where patients can answer surveys (i.e. NCI PRO-CTCAE survey items) and receive symptom management advice tailored to symptom severity, 2) a web-based clinician dashboard where staff track patients' symptoms and steps, and communicate with patients, and 3) an administrative website where program content can be managed and generated.

Through the SMART app, patients track their symptoms daily through surveys and then receive tailored symptom management advice based on their reported symptoms. Patients can also track their steps, sleep and heart rate, and communicate with their study team directly through the app. The SMART platform also includes a clinician dashboard and admin site where nurses, providers, and other study team members can login to view and manage patients enrolled to the study. The console also allows study staff to monitor the severity and frequency of symptoms patients are reporting throughout the day, view patient steps, collect patient survey response data, send reminders to patients, and assign program content.

The Beiwe app will be used to passively collect information about participants. Passive data collection is essential because mobile health interventions that require significant patient involvement tend to have higher rates of attrition, and patients' illness may interfere with their ability to report their symptoms. It is essential to develop an intervention that can be utilized to detect patients' symptoms or anomalies in their behaviors with minimal involvement. Rapid identification and management of symptoms can improve patients' quality of life and other disease related outcomes. We anticipate the remote monitoring of patient symptoms using both the SMART app and Beiwe app will allow us to better understand cancer patients' behaviors and relate them to clinically significant patient symptoms and outcomes. The intervention combination may also provide a method for better identifying clinically meaningful anomalies in cancer patients' behaviors.

5.31a Software and Data Collection Features

The SMART app employs similar features and data collection methods used in the aforementioned studies and protocols. Please see *SMART App Features and Screenshots: Patient Guide* (Appendix 5) for descriptions of the app's features, including: log-in screen, symptom management advice, connecting to Fitbit device/Apple Health/Google Fit, notifications, surveys, the "Call My Clinician" function so that patients can contact their clinical teams without searching for numbers, and general app navigation.

As noted above, the SMART app collects active data from participants' survey responses and wearable accelerometer, connected to the platform with patient permission. Active data are collected while a patient is using the app (e.g. responding to survey questions). Information regarding data collection and privacy measures for the SMART app is located in *SMART App Data Privacy and Security* (Appendix 7). The Beiwe smartphone app collects passive data from participants' phone usage, with participant consent, continuously without patient input. Participant interaction with the Beiwe app consists of installing the app and keeping it running in the background of their phone; all data is collected in the background. Specifically, as noted in the *Beiwe App Data Privacy and Security* (Appendix 10) the app collects passive data, including: mobility traces, consisting of flights (linear segments of movement) and pauses (times of no movement) which are constructed from GPS data; and summary statistics of phone communication (calls and text messages) patterns, simple examples being the total number of communication events in a time period (e.g., 1 week), the total number of

communication partners, and reciprocity of communication (defined as the difference between outgoing communication volume and incoming communication volume).

Since passive data collection does not require participant input, the study team has put a safeguard in place for the Beiwe app to ensure participants log into their app at least once a week. Participants will receive bi-weekly push notifications from the Beiwe app containing a positive affirmation. The brief quote will serve as a reminder for participants to log in to the Beiwe app and make sure that it is still running properly on their phone.

5.31b Symptom Management

The SMART app is designed to collect and assess participants' toxicities and symptoms on chemotherapy treatment in between visits with their clinician. Participants report the severity of their symptoms via a brief in-app survey of PRO-CTCAE items. The app then determines a symptom's risk level and necessary response, which is either to provide no intervention, tailored symptom management advice, or an alert to call the clinician. Figure 3 provides a more detailed overview of this process.

The symptom response criteria and the *Symptom Management Content* (Appendix 2) were developed by research staff in cooperation with the oncology providers at Dana-Farber. The study PI, who is also a practicing gynecologic oncologist, collated reputable and trusted sources, such as ASCO, the National Cancer Institute, the American Cancer Society, Cancer Care Ontario, and the Dana-Farber Cancer Institute, to create the content for each symptom, which includes: symptom management advice, questions to ask the clinical team, and multimedia content for participants to actively engage in symptom management practices. The content and response criteria were then reviewed and refined by study investigators, research staff, and gynecologic oncology clinicians to produce the final versions.

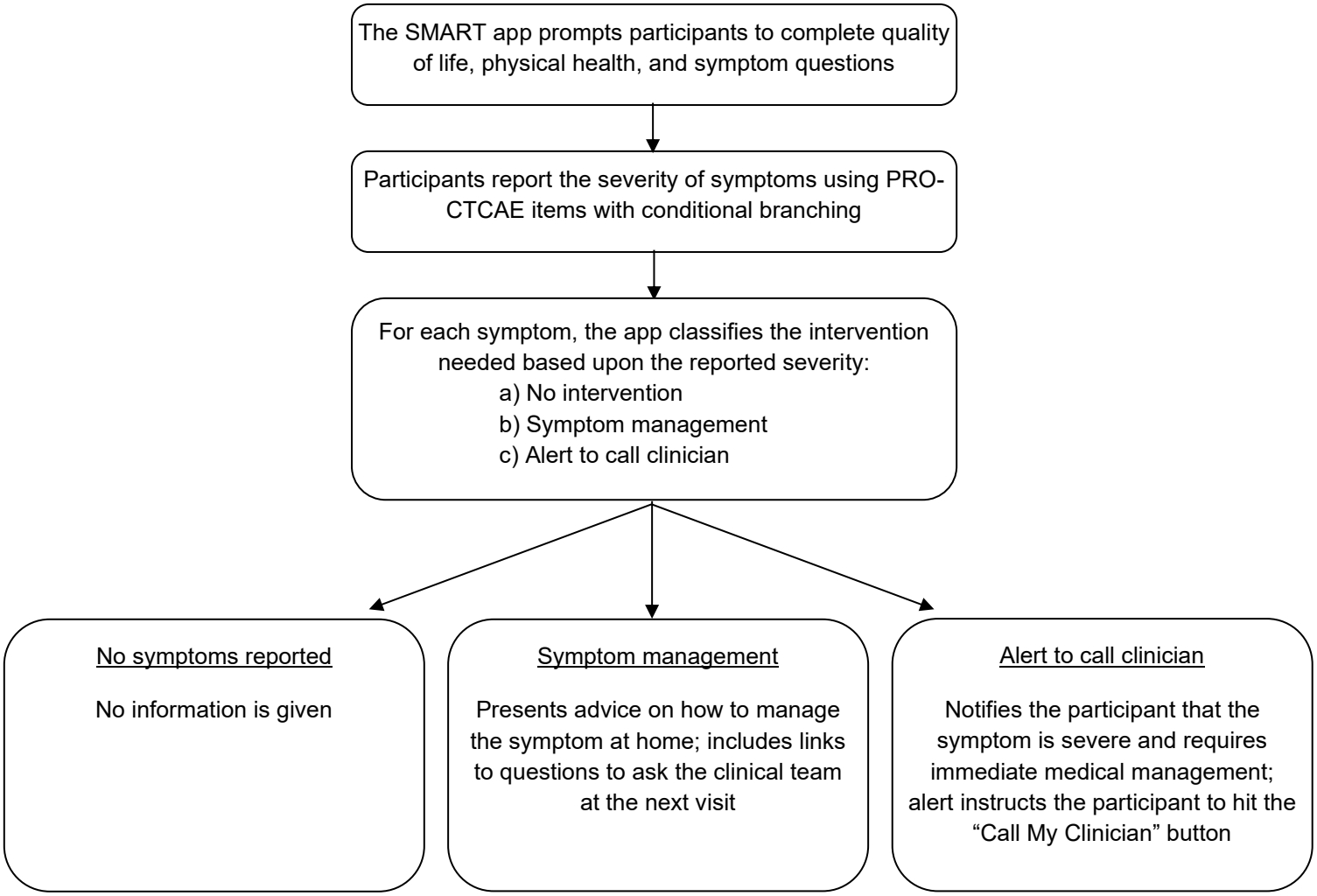
If, over the course of the study, participants identify a need to access static versions of the patient education materials outside of the smartphone app, the study team will create a website which will contain static patient education materials about the symptoms that are targeted in the SMART App. This website will present evidence-based information on symptom education and symptom management. Some of the content on the website will mirror the content in the symptom management app, while other information will be housed only on the website. The purpose of the website would be to provide a centralized location for patients to find symptom education and symptom management information at any time they might be experiencing low-level symptoms. Content will be created by the study PI (a practicing medical oncologist at Dana-Farber Cancer Institute) and the study team, and will include information from trusted sources listed above.

5.32 Wearable Fitness Tracker

The Fitbit Charge 3 is an accelerometer that is worn on the wrist and tracks users' heart rate continuously in addition to steps, distance, and calories. The addition of an optimal heart rate sensor

enables monitoring of the time that the tracker is being worn (i.e. adherence).[48,49] Wrist-worn activity trackers have been shown to accurately measure heart rate when compared with electrocardiography,[50,51] have good test-retest reliability (intraclass correlations of 0.75-0.95)[52] but over count steps compared with the gold standard ActivPAL in free-living conditions due to the variability in limb-specific activities.[53] One of the advantages of the Fitbit Charge 3 is it allows for close monitoring of adherence to the device over time because of its continuous measurement of heart rate. Additionally, the device has a long battery life and looks like a traditional wristwatch which may make participants more likely to adhere to the device when compared with other wearable fitness trackers. The disadvantages include: it may be less accurate if the participant is dependent upon a device for ambulating (e.g., cane or walker) or wears the device on her non-dominant arm. [51, 54] The Fitbit data will be stored on participants' devices and smartphones, consistent with the commercially available devices, and also uploaded to the RMDY SMART site.'

Figure 3. Symptom classification and response in the SMART app intervention



5.4 Data Collection

Table 2 specifies the instrument and intervention data collection timelines during each study phase. Intervention data will be collected continuously during enrollment.

Table 2. Instrument data collection across study timeline

		DAY		
		Visit 0	1-89	Visit 90
INSTRUMENT	Participant Baseline Interview	□		
	Participant Post-Baseline Interview			□
	Health/Tx Info	□		□
	Healthcare Utilization & Call Log			□
	Debriefing Interviews			□
	QoL, PF, and Symptom Questions		□	
	Physical Function Survey		□	
	Medical Care Resource Form			□
	Passive App Data	□	□	□
	Accelerometer Data	□	□	□

Data obtained via interviews, surveys and chart abstractions will be stored on the Harvard REDCap server and hard copies will be stored in secure, restricted-access locations. Data obtained via the smartphone apps and Fitbit will be stored on the RMDY and Beiwe research platforms.

RMDY follows industry-adopted best practices and regulatory requirements for digital therapeutics applications. The RMDY platform is fully compliant with HIPAA and GDPR. All applications are hosted in Microsoft Azure datacenters, offering enterprise-level security, availability, scalability, and compliance. All data hosted in the RMDY platform is encrypted “at rest” using AES256 encryption, and “in transit” using TLS 1.2. The organization is also currently undergoing a third-party assessment for HiTrust certification, which demonstrates compliance with, and adherence to, globally-recognized standards, regulations, and business requirements – including ISO, NIST, PCI, GDPR, HIPAA and various state laws.

The Beiwe App will employ the same data privacy and security processes used in IRB approved protocols across four Partners Institutions (DFCI Protocol # 16-477; BIDMC Protocol #: 2015P-000240; McLean Hospital Protocol #s: 2015P001303, 2015P001538, 2012P000890, 2015P002189; MGH Protocol #: 2015P000666**)**. Although the app collects a large amount of data, it was custom-built to be used in a health care setting and includes robust security and privacy features to safeguard all data and protect participants’ privacy, including data anonymity, participant authentication, and data encryption. SMART App Data Privacy and Security (Appendix 7) and Beiwe App Data Privacy and Security (Appendix 10) describe these processes in detail.

5.5 Description of Study Process

Study procedures are outlined below. Based on the study team's experience conducting pilot studies, we understand that piloting minimal-risk interventions across sites with varying institutional policies and patient populations must be flexible in order to ensure that the study can quickly adapt to patient needs as we learn more about them over the course of the study. The study activities currently outlined in the protocol therefore may be adapted without the submission of an amendment in cases where these modifications would pose no additional risk to patients, as determined by the overall PI of the study.

5.51 Instrument Administration

Participant Baseline Survey:

- Participants will complete a baseline survey when they begin study interventions (Appendix 14).
- All data from the interview will be stored in RedCap; if paper copies are used, they will be stored in restricted-access locations.
- Estimated time to completion: 45 minutes.

Participant Post-Baseline Survey:

- Participants will complete a post-baseline survey approximately three months after the intervention was administered, as close to the 3-month projected assessment date as possible (Appendix 15).
- All data from the interview will be stored in RedCap; if paper copies are used, they will be stored in restricted-access locations.
- Estimated time to completion: 30 minutes.

App-Based Surveys:

- Participants will be prompted by the SMART app to complete the survey.
- The surveys will consist of measures of global quality of life, physical health, PRO-CTCAE questions for 10 symptoms, and an additional question designed to query severe symptoms.
- Survey items will not interfere with participants' use of their phone.
- Symptom surveys are administered daily, and the participant cannot take the symptom survey more than once per day. Quality of life surveys will be given over the weekend. Patients can also submit responses less frequently. Once the participant completes the survey it is removed from their action list. Missed surveys do not remain on the patient's action list and can be completed at the next survey timepoint, as applicable.
- Estimated time to completion: 2-3 minutes.
- Participants and their oncology providers will be given summaries of their survey responses throughout the study through HIPAA-compliant secure email. Patients and clinicians may also choose to have their survey responses mailed to them via priority mail or to receive hard copies.

Debriefing Interview:

- Study staff will aim to conduct debriefing interviews with the first few participants enrolled at each site and a purposively sample a subset of patients who enroll later (up to 15 total).
- Debriefing interviews will be administered by study staff following participants' completion of the final post-baseline survey.
- Study staff will discuss the debriefing interviews to identify opportunities for protocol improvement.

- Estimated time to completion: 20 minutes

Health/Treatment Chart Abstraction:

- Study staff will review participants' medical charts to complete the Health/Tx Information form for the time-points of participants' baseline and post-baseline visits.

Health Care Utilization Chart Abstraction:

- Study staff will review participants' medical charts to complete the Health Care Utilization form after participants' post-baseline visit.
- Patients will complete the Medical Care Resource Form to capture all health care utilization during the study, including care outside of affiliated sites that may not be captured in site medical records.

5.52 Intervention Administration

5.52a Smartphone Apps

Instructional Session:

- On Day 0, participants will download, install, and run the SMART and Beiwe apps on their personal smartphones, with assistance from study staff as needed. Participants will receive step-by-step instructions and login information for the apps (SMART App Installation Information is included in SMART App Features and Screenshots (Appendix 5); Appendix 12: Beiwe App Installation Guide iOS and/or Appendix 13: Beiwe App Installation Instructions for Android).
- Participants are registered to the SMART App by a study team member that has access to the clinician dashboard and admin site. Study staff will create an account for the participant by using their mobile phone number. When the participant opens the SMART App, they will be required to login using two-step verification. First, participants will be promoted to enter their mobile number. Next, they will have to enter a 4-digit personal validation code that will be automatically sent to their smartphone via SMS. The app does not ask the subject to enter any personal information (name, date of birth, etc.) and cannot be directly linked to their health records.
- Participants will register in the Beiwe App by using a unique User ID and temporary password and then choose a new password. The subject will be assigned a unique 8-character Participant ID which consists of mixture of numbers and letters. The app does not ask the subject to enter any personal information (name, date of birth, phone number, etc.) and cannot be directly linked to their health records.
- Participants will enter their oncology providers' phone numbers for the "Call my Clinician" button and enter study staff's contact number for the "Call Research Assistant" button.
- At the end of the registration process for Beiwe, the participant will click a button to acknowledge that she has reviewed the privacy information with the RA and provide in-app consent.
- The RA will then review how to use the apps and participants will be given a copy of the SMART App Participant Guide (Appendix 5) and the Beiwe App Participant Guide (Appendix 8) and Summary Sheet for Participants (Appendix 3) which describes the apps and provides directions on how to use its features, frequently asked questions, information regarding Beiwe positive affirmation push notifications, as well a review of the data that is collected and privacy measures.

Symptom Management:

- Participants will be prompted daily to answer questions about 10 unique symptoms via the SMART App in the Symptom Survey. If a participant is not experiencing any symptoms that day, they can select “not-applicable”. Over the weekend participants will be administered quality of life surveys (the FACT-G7 and PROMIS Physical Function short form 6b).
- If a participant reports one or more low-risk toxicities, the app will present tailored advice on how she can manage each symptom at home. If participants report high-risk toxicities, they will be instructed that they have reported a toxicity that requires further management from their clinical team and are given the instruction to call their clinician. Their clinician’s phone number will be listed within the SMART app so that it is easily accessible for participants’ use. Please refer to Figure 3 for an overview of this process.
- In order to ensure participant safety, the RAs and apps will emphasize to participants that survey results **will not** be reviewed by a clinician in **real-time**. Thus, surveys cannot be used in place of communicating with clinicians to request help. The reminder will also note that if the participant feels unsafe, she should contact the treating clinician directly.
- Participants and their oncology providers will be given a graphical summary of the symptoms participants reported by participants in-between visits. This is dependent on patient adherence –e.g. if a patient is not using the smartphone application and we are unable to receive symptom data, we will not have data to share with patients or their clinicians and no summary sheet will be provided. See Appendix 4: Sample Clinical Summary Sheet for an example of what the summary data will look like. We will not monitor whether clinicians use the summary sheets, since it is difficult to reliably capture what providers read and absorb.

5.52b Troubleshooting the SMART App

The intervention’s participant guides outline common troubleshooting issues and how to solve them. Participants will be instructed to call study staff as soon as possible to report if they are having trouble using the app.

5.52c Fitness Tracker

All participants will also receive a Fitbit Charge 3 wearable fitness tracker.

Instructional Session:

- Following the completion of the Participant Baseline Survey on Day 0, participants will set up their fitness tracker, with assistance from study staff as needed. Participants will learn how to use the fitness tracker; download the Fitbit smartphone app; learn how to synchronize their device to their smartphone; and work with study staff to synchronize their accelerometer data to the research database.
- In addition to the accelerometer, participants will receive the *Fitbit Participant Guide* (Appendix 11), which describes proper wear and care, charging and battery life, troubleshooting instructions, uploading data, and compliance.
- Participants will be encouraged to contact study staff at any time with questions or issues to help ensure proper wear and use of the fitness tracker.

Tracking Devices:

- The accelerometer assigned to each participant will be tracked according to the product serial number and assigned unique ID number.
- Participants will be allowed to keep the accelerometer as a token of appreciation for their participation in the study, and to minimize potential transmission of skin infections (e.g. methicillin-resistant Staphylococcus aureus) between participants.

Monitoring

- If patients are wearing their accelerometer continuously throughout the day and experience a severe drop in steps (e.g. ≤1,000 steps in a 24-hour period) that is unlikely to be attributable to external factors (e.g., severe snowstorm or rain), study staff will contact the patient to ask if she is experiencing severe symptoms.

5.52d Apps and Fitness Tracker Use and Compliance

Participants will be instructed to avoid adjusting app settings (for Fitbit, SMART, and Beiwe Apps), to ensure data is collected. If the study team does not receive data from the SMART or Beiwe Apps or fitness tracker, study staff will attempt to contact patients to help resolve the issue remotely or during an upcoming clinic/study visit.

5.52e Subsequent Enrollment in a Therapeutic Drug Trial

Participants in this study may enroll in a therapeutic drug trial at any point after signing consent to participate in this study. However, if a patient enrolls in a therapeutic drug trial that requires structured symptom or toxicity reporting we will record this and perform a sensitivity analysis, excluding any patients who participated in a therapeutic trial after enrollment, to determine whether this impacts our findings. Since this is a feasibility and acceptability trial, we do not want to censor participants.

5.53 Compensation

If site policies permit, patients will be provided with a gift-card, Clincard or equivalent valued at $50 after completing the baseline and post-baseline interviews, to thank patients for their time participating in the study and to minimize attrition. Additionally, participants may be reimbursed for significant study-related expenses (e.g., expenses >$25 directly attributable to the cost of uploading data from the smartphone app over a cellular data plan) if site policies allow.

5.6 Adverse Reactions and Management

5.61 Reporting Adverse or Unanticipated Events

Potential adverse events (AE) for this project are expected to be all non-medical in nature. There is a small chance that participants could worsen repetitive use injuries (e.g., carpal tunnel syndrome) while using the smartphone app. Subjects may experience mild anxiety when answering survey questions about emotional issues or questions about coping challenges or difficulties related to discussing the subject matter. The PI will report unanticipated and serious adverse events to the IRB in a timely manner on an ongoing basis. For the purpose of this study a Serious Adverse Event (SAE) is defined as an event that, as a direct result of the study, causes serious harm to the subject (e.g., hospitalization).

5.62 Anticipated Reactions & Reaction Management

Should participants become exceedingly upset, disoriented or fatigued or need to attend to matters of personal care during the surveys, study staff will ask the subject if they would like to take a break or reschedule the survey for another time. In the event that participants experience distress while completing surveys, we will follow standard procedures used in our behavioral health intervention studies for counseling and referral. The PI will be notified immediately, and participants will be provided with the pager numbers for both the study PI and a clinician at the primary site, who will evaluate any participants who are distressed for risk of imminent danger and refer them to appropriate services if they are needed.

6.0 STATISTICAL ANALYSIS

6.1 Primary and Secondary Endpoints

Primary Endpoints

1) Feasibility of the SMART intervention
2) Acceptability of the SMART intervention

Secondary Endpoints

2) Perceived efficacy
3) Additional patient outcomes, including: health-related quality of life, anxiety and depression, symptom burden, and health care utilization
4) Agreement between patient and physician estimates of performance status
5) Correlation between data collected from the wearable and smartphone accelerometers
6) Predictive ability of wearable accelerometer and smartphone data for patient's performance status and clinically significant events

6.2. Sample Size

The primary objective of this study is to assess the feasibility and acceptability rates of the SMART intervention. A convenience sample of 30 patients will be enrolled to the study, with expected accrual of approximately 15 patients each at a maximum of 2 community oncology sites.

6.3 Analysis Plan

Statistical analysis will be descriptive in nature and will access feasibility, acceptability, and perceived efficacy, as well as estimate outcomes parameters.

Feasibility: Feasibility will be defined as ≥50% approach-to-enrollment rate among eligible participants, and 2) ≥50% 3-month adherence rates to the smartphone app and wearable accelerometer (based upon attrition rates from prior trials of PROs).[10] Patients who complete daily surveys ≥4 days per week over the three-month study period will be considered as adherent to the smartphone app. Patients who wear the wearable accelerometer ≥4 days per week over the three-month study period will be considered as adherent to the wearable accelerometer.

Acceptability: Acceptability will be defined as ≥60% of participants "agree" or "strongly agree" that they "would recommend the SMART Study to other patients with cancer receiving chemotherapy;" and <30% of participants answering agree or strongly agree to either question: 1) "Participating in this study placed a substantial burden on me" and 2) "I wish I had not agreed to participate in this study."

Perceived efficacy: Perceived efficacy will be measured by qualitative analysis. We will conduct debriefing interviews with approximately 30 participants and their clinicians (evenly distributed among the community oncology sites) to obtain information about the acceptability of the intervention and recommendations for any modifications to improve any aspects of recruitment, enrollment, education, the timing of study assessments, graphical display of information, and the app that could be improved.

Patient outcomes: We will collect baseline and 3-month outcome data from patient interviews and clinician surveys. At each time point clinicians and participants will be asked to rate the participant's ECOG performance status and EuroQoL EQ-5D index; patients will also be asked to rate their symptoms using the PRO-CTCAE. We will also collect health care utilization data (e.g. nursing calls, emergency department visits, hospitalizations, and hospice referrals) from the medical chart and healthcare utilization logs provided by patients. For purposes of estimating outcomes parameters, the distributions of these patient outcomes will be summarized using descriptive statistics such as means, standard deviations, and proportions, and, where appropriate, cumulative incidence functions. Additional demographic information that will be summarized include age, marital status, race/ethnicity, education, household structure, income, employment, health literacy and numeracy, and cancer treatment associated burden. We will abstract information from the medical chart; e.g., comorbid health conditions, prior chemotherapy regimens, and time since diagnosis.

Correlative analyses:

Agreement between patient-oncologist estimates of performance status will be estimated by Cohen's Kappa statistic. We will descriptively summarize correlations between active (e.g. quality of life and symptoms) and passive (e.g. time spent away from home) data collected from the SMART and Beiwe apps and the wearable accelerometer (average daily steps) with clinical outcomes collected at baseline and post-baseline (i.e. performance status, quality of life, and symptoms assessment as obtained from the PRO-CTCAE and CTCAE). In addition to descriptive analyses and estimating correlations between passive smartphone data and clinical outcomes, passive data may contain information that allows for the prediction of future clinically-relevant events, such as visits to the emergency department, urgent clinic encounter, or hospitalization. By testing for changes in activity, mobility, and social patterns over time as measured through smartphone use may be able to identify significant anomalies in patient behavior in the days prior to relapse. In a study in a cohort with schizophrenia, behavioral anomalies detected in the two weeks prior to clinical relapse occurred at a rate 71% higher than anomalies detected on other days.[55] The method is based on a modification of the Hotelling's T test to detect changes in the distribution of previous passively-measured activity. In our proposed study, this method might be used to query patients in real time to detect if an unscheduled clinical event might occur in the near future.

7.0 REFERENCES

1. Di Maio M, Gallo C, Leighl NB, et al: Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 33:910-5, 2015

3. Montemurro F, Mittica G, Cagnazzo C, et al: Self-Evaluation of Adjuvant Chemotherapy-Related Adverse Effects by Patients With Breast Cancer. JAMA Oncol:1-8, 2015

4. Sorensen JB, Klee M, Palshof T, et al: Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer 67:773-5, 1993

5. Hutchinson TA, Boyd NF, Feinstein AR, et al: Scientific problems in clinical scales, as demonstrated in the Karnofsky index of performance status. J Chronic Dis 32:661-6, 1979

6. Blagden SP, Charman SC, Sharples LD, et al: Performance status score: do patients and their oncologists agree? Br J Cancer 89:1022-7, 2003

7. Dajczman E, Kasymjanova G, Kreisman H, et al: Should patient-rated performance status affect treatment decisions in advanced lung cancer? J Thorac Oncol 3:1133-6, 2008

8. Ando M, Ando Y, Hasegawa Y, et al: Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. Br J Cancer 85:1634-9, 2001

9. Detmar SB, Muller MJ, Schornagel JH, et al: Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA 288:3027-34, 2002

10. Basch E, Deal AM, Kris MG, et al: Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 34:557-65, 2016

11. Basch E, Artz D, Dulko D, et al: Patient online self-reporting of toxicity symptoms during chemotherapy. J Clin Oncol 23:3552-61, 2005

12. Torous J SP, Shanahan M, Lin C, Peck P, Keshavan M, Onnela JP: Utilizing a personal smartphone custom app to assess the Patient Health Questionnaire-9 (PHQ-9) depressive symptoms in patients with major depressive disorder. JMIR Mental Health 2:e8, 2015

13. ClinicalTrials.gov: The HOPE Trial: Helping our Patients Excel, 2017

14. Wright AA RN, Staples P, Schonholz S, Cronin A, Carlson K, Keating NL, Onnela JP: The HOPE Pilot Study: Harnessing Patient-Reported Outcomes and Biometric Data to Enhance Cancer Care. JCO Clinical Cancer Informatics

15. Basch E, Wood WA, Schrag D, et al: Feasibility and clinical impact of sharing patient-reported symptom toxicities and performance status with clinical investigators during a phase 2 cancer treatment trial. Clin Trials, 2015

16. Bennett AV, Reeve BB, Basch EM, et al: Evaluation of pedometry as a patient-centered outcome in patients undergoing hematopoietic cell transplant (HCT): a comparison of pedometry and patient reports of symptoms, health, and quality of life. Qual Life Res 25:535-46, 2016

17. Maddocks M, Wilcock A: Exploring physical activity level in patients with thoracic cancer: implications for use as an outcome measure. Support Care Cancer 20:1113-6, 2012

18. Dahele M, Skipworth RJ, Wall L, et al: Objective physical activity and self-reported quality of life in patients receiving palliative chemotherapy. J Pain Symptom Manage 33:676-85, 2007

19. Skipworth RJ, Stene GB, Dahele M, et al: Patient-focused endpoints in advanced cancer: criterion-based validation of accelerometer-based activity monitoring. Clin Nutr 30:812-21, 2011

20. Ohri N, Kabarriti R, Bodner WR, et al: Continuous Activity Monitoring During Concurrent Chemoradiotherapy. Int J Radiat Oncol Biol Phys 97:1061-1065, 2017

21. Enzinger AC, Wind JK, Frank E, et al: A stakeholder-driven approach to improve the informed consent process for palliative chemotherapy. Patient Educ Couns, 2017

23. EuroQol G: EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 16:199-208, 1990

24. Janssen MF, Pickard AS, Golicki D, et al: Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 22:1717-27, 2013
25. Kim SH, Kim HJ, Lee SI, et al: Comparing the psychometric properties of the EQ-5D-3L and EQ-5D-5L in cancer patients in Korea. Qual Life Res 21:1065-73, 2012
26. Sullivan PW, Ghushchyan V: Mapping the EQ-5D index from the SF-12: US general population preferences in a nationally representative sample. Med Decis Making 26:401-9, 2006
27. Pickard AS, Neary MP, Cella D: Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 5:70, 2007
28. Cella D, Riley W, Stone A, et al: The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 63:1179-94, 2010
29. Hays RD, Bjorner JB, Revicki DA, et al: Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. Qual Life Res 18:873-80, 2009
30. Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-55, 1982
31. Basch E, Iasonos A, Barz A, et al: Long-term toxicity monitoring via electronic patient-reported outcomes in patients receiving chemotherapy. J Clin Oncol 25:5374-80, 2007
32. Lowe B, Kroenke K, Herzog W, et al: Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord 81:61-6, 2004
33. Thekkumpurath P, Walker J, Butcher I, et al: Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer 117:218-27, 2011
34. Johns SA, Kroenke K, Krebs EE, et al: Longitudinal comparison of three depression measures in adult cancer patients. J Pain Symptom Manage 45:71-82, 2013
35. Spitzer RL, Kroenke K, Williams JB: Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 282:1737-44, 1999
36. Basch E, Jia X, Heller G, et al: Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst 101:1624-32, 2009
37. Dueck AC, Mendoza TR, Mitchell SA, et al: Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). JAMA Oncol 1:1051-9, 2015
38. Spitzer RL, Kroenke K, Williams JB, et al: A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166:1092-7, 2006
39. Lowe B, Decker O, Muller S, et al: Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 46:266-74, 2008
40. Andersen BL, DeRubeis RJ, Berman BS, et al: Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 32:1605-19, 2014
41. Lyons KD, Bakitas M, Hegel MT, et al: Reliability and validity of the Functional Assessment of Chronic Illness Therapy-Palliative care (FACIT-Pal) scale. J Pain Symptom Manage 37:23-32, 2009
42. Wallace LS, Rogers ES, Roskos SE, et al: Brief report: screening items to identify patients with limited health literacy skills. J Gen Intern Med 21:874-7, 2006
43. Bakke E: A Model and MEasure of Mobile Communication Competence. Human Communication Research 36:348-371, 2010
44. Austenfeld JL, Stanton AL: Writing about emotions versus goals: effects on hostility and medical care utilization moderated by emotional approach coping processes. Br J Health Psychol 13:35-8, 2008
45. Low CA, Stanton AL, Bower JE, et al: A randomized controlled trial of emotionally expressive writing for women with metastatic breast cancer. Health Psychol 29:460-6, 2010
46. Carver CS: You want to measure coping but your protocol's too long: consider the brief COPE. Int J Behav Med 4:92-100, 1997

47. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373-83, 1987
48. Kurti AN, Dallery J: Internet-based contingency management increases walking in sedentary adults. J Appl Behav Anal 46:568-81, 2013
49. Evenson KR, Goto MM, Furberg RD: Systematic review of the validity and reliability of consumer-wearable activity trackers. Int J Behav Nutr Phys Act 12:159, 2015
50. Wallen MP, Gomersall SR, Keating SE, et al: Accuracy of Heart Rate Watches: Implications for Weight Management. PLoS One 11:e0154420, 2016
51. de Zambotti M, Baker FC, Willoughby AR, et al: Measures of sleep and cardiac functioning during sleep using a multi-sensory commercially-available wristband in adolescents. Physiol Behav 158:143-9, 2016
52. Kooiman TJ, Dontje ML, Sprenger SR, et al: Reliability and validity of ten consumer activity trackers. BMC Sports Sci Med Rehabil 7:24, 2015
53. Atallah L, Lo B, King R, et al: Sensor positioning for activity recognition using wearable accelerometers. IEEE Trans Biomed Circuits Syst 5:320-9, 2011
54. Cadmus-Bertram L, Marcus BH, Patterson RE, et al: Use of the Fitbit to Measure Adherence to a Physical Activity Intervention Among Overweight or Obese, Postmenopausal Women: Self-Monitoring Trajectory During 16 Weeks. JMIR Mhealth Uhealth 3:e96, 2015
55. Barnett I, Torous J, Staples P, et al: Relapse Prediction in Schizophrenia through Digital Phenotyping: A Pilot Study. Journal of the American Medical Informatics Association Submitted

8.0 APPENDICES

Recruitment/Enrollment:

Appendix 1: Registration Form

Interventions:

Appendix 2: Symptom Management Content
Appendix 3: Summary Sheet for Participants
Appendix 4: Sample Clinical Summary Sheet
Appendix 5: SMART App Features and Screenshots: Patient Guide
Appendix 6: SMART Study Clinician Dashboard
Appendix 7: SMART App Data Privacy and Security
Appendix 8: Beiwe App Participant Guide
Appendix 9: Beiwe App Info for Study Team
Appendix 10: Beiwe App Data Privacy and Security
Appendix 11: Fitbit Participant Guide
Appendix 12: Beiwe App Installation Guide: iOS
Appendix 13: Beiwe App Installation Guide: Android

Instruments:

Appendix 14: Participant Baseline Interview
Appendix 15: Participant Post-Baseline Interview
Appendix 16: SMART App Survey
Appendix 17: Health/Tx Information
Appendix 18: Health Care Utilization
Appendix 19: Call Log
Appendix 20: Patient Debriefing Interview
Appendix 21: Clinician and Site Staff Debriefing Interview

Other:

Appendix 22: Data and Safety Monitoring Plan
Appendix 23: Reimbursement Sheet
Appendix 24: Beiwe Positive Affirmation Push Notifications
Appendix 25: Consent Form Template