HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: Assessing the feasibility of a patient-centered activity regimen in patients with lung cancer.

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(*If applicable*) Clinicaltrials.gov Registration #: NCT03352245

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INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

The first phase of this study was performed at the Medical University of South Carolina (MUSC) and established the feasibility of monitoring physical activity in patients with advanced stage lung cancer via a FitBit® (San Francisco, CA) accelerometer for one week.[1] Though feasibility was established with monitoring for 1 week, when the monitoring period was extended to 4 weeks, both data collection and adherence fell significantly.

In this Phase 2 of the project, we will evaluate the feasibility of implementing a low-intensity, patient-centered activity regimen (PCAR) that prioritizes education and communication over a 12-week period in advanced stage lung cancer patients. Our primary outcomes will include number of patients increasing their overall step count over the study period and adherence to step count recommendations. Secondary outcomes will include quality of life (QoL), dyspnea, and depression scores before and after the intervention as well as a patient feedback questionnaire (to guide further interventions). There will also be a blood draw before and after the intervention to analyze biomarkers related to lung cancer. Our goals are to increase overall step count and obtain adherence of ≥50%.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

We estimate the project's duration at 16 months. At MUSC, n=15 subjects were enrolled between August 2016 and May 2017 (10 months). Using the same rate of enrollment, with 2 sites we estimate enrolling 3 patients/month. We estimate ~13 months to enroll the remaining 40 subjects. We have added an additional 3 months to ensure all data is collected and to perform data analysis.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Background:

Despite increasing treatment options, lung cancer remains second in cancer frequency and first in cancer mortality.[2] It is also one of the most burdensome cancers, with patients having more symptoms, lower activity, and worsened QoL than their healthy counterparts.[3] As might be expected, patients' symptoms and activity levels worsen with time and treatment.[4] The pattern of symptom progression is consistent with the concept of the "dyspnea spiral" in patients with chronic lung disease, wherein dyspnea develops, activity is avoided, functional capacity is lost, and dyspnea worsens. A recent review showed that physical activity studies in lung cancer patients are limited but overall suggest benefit.[3] In addition, despite a heavier symptom burden,[5] patients with advanced stage disease are less frequently studied. Survey data reveals that stage III and IV lung cancer patients prefer to receive activity guidance from their oncologist,[6] and a recent retrospective study of lung cancer survivors showed that approximately 80% of patients requesting exercise recommendations would prefer walking.[7] Unfortunately, physical activity recommendations by clinicians are infrequent.[6]

Though likely beneficial, activity studies in lung cancer patients show low adherence in both early and advanced disease,[8,9] and prior studies have accepted exercise adherence of 50-70%.[10,11] Interestingly, clinicians treating chronic obstructive pulmonary disease (COPD) are using pedometers to predict exacerbations,[12] predict clinical outcomes,[13] and assess changes in QoL.[14,15] Accelerometer use in patients with lung cancer is

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infrequently studied, practical, has the advantage of objectively monitoring low-impact physical activity, and has the potential to improve adherence to physical activity recommendations. In summary, lung cancer patients are interested in exercise though research and clinical application are infrequent. If a clinically practical regimen that improves activity adherence can be identified, clinical benefit in lung cancer is likely. Step counting with digital monitoring and tailored messaging may achieve this goal.

Significance:

Since lung cancer patients with advanced stage disease have higher symptom burden and more activity impairment, this population may obtain more benefit from increased physical activity than patients with early stage disease. However, little data is available regarding physical activity or the clinical utility of using accelerometers with an exercise prescription in patients with advanced stage lung cancer. Success of this study would establish a real-world, implementable, low-impact activity regimen that improves QoL in lung cancer patients.

Preliminary Studies:

Our phase I study collected data for 7 days in 30 patients.[1] Most patients were interested in participating in the physical activity study and strongly positive Spearman Rank correlation between step count and overall QoL (ρ=0.46), physical functioning (ρ=0.61), and emotional functioning (ρ=0.40) as well negative correlation between step count and depression (ρ =-0.40), dyspnea (ρ=-0.54), and pain (ρ=-0.37) were noted. Patients with higher step counts had higher QoL scores and lower symptom and depression scores (see Figures 1, 2, and 3).

Without changing our design, we collected 4 weeks of step count data in 29 patients using an escalating regimen (see activity regimen below). Communication with subjects during the 4-week period was inconsistent. In this cohort, 21% (6/29) of patients did not use the device. Of those who used the device 61% (14/23) increased their weekly step count at some point during the 4 week period, though weekly prescriptions were followed in <50% of cases (unpublished). Patient participation during this 4-week period may have been too low to have a therapeutic benefit. To improve patient participation and adherence to activity prescriptions, we will (1) **provide an educational session** at enrollment, (2) **increase subject communication** via tailored electronic messaging, and (3) **utilize a wrist-bound device** (FitBit Flex 2) rather than one clipping to clothing (FitBit Zip).

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Study Design

Randomized trial enrolling n=40 patients (Usual care: n=20; Intervention group: n=20).

Randomization: Participants will be randomized into one of 2 study arms using a random permuted block design of varying block size in a 1:1 ratio (n=20 to intervention, 20 to usual care). Since the study utilizes text messaging as an intervention, blinding will not be possible.

Definitions

Intervention Group will receive the interventions mentioned above, including an educational session at enrollment, tailored electronic messaging with walking goals, and a wrist-bound accelerometer.

Usual care group will receive standard of care management from their Oncologist.

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Exercise Adherence will be defined as (the number of weeks a subject follows the activity prescription)/(the number of "usable" weeks). As per the literature, a week is considered "usable" if 5/7 days of step counts are available, and days with <200 steps/day are considered not usable. Thus, not all weeks will have enough data to provide an appropriate average daily step count nor a prescription. Our goal is to obtain >50% exercise adherence.

Inclusion/Exclusion Criteria

Inclusion criteria:

- Pathologic evidence of any stage non-small cell stage lung cancer (NSCLC)
- Approval of the treating clinician
- Adult patients (age >21 years) willing to wear a FitBit® device (FitBit, Inc., San Francisco, CA)
- Access to a smartphone, agree to receive twice/daily text messages for 12 weeks (including any costs), and willingness to download the FitBit application to their smartphone.
- Low activity level as judged by a brief physical activity questionnaire (i.e., <150 minutes/week of moderate-intensity exercise, <75 minutes/week of vigorous aerobic exercise, or an equivalent combination).

Exclusion criteria:

- Memory impairment (as judged by the treating clinician)
- Communication impairment (as judged by the treating clinician)
- Treating clinician's request not to alter physical activity
- Physical inability to safely walk (as judged by the treating clinician)

The FitBit® Flex 2 device is a convenient accelerometer that is worn on the wrist and wirelessly synchronizes with smartphones. FitBit® devices have been validated in COPD patients,[16] and the accuracy is similar to other wearable pedometers.[17]

Patients with lung cancer are eligible regardless of the timing of therapy. That is, patients who are diagnosed but before treatment, currently receiving treatment, survivors, or long-term survivors are eligible. Since this study focuses on adherence to an intervention, fallout patients will not be replaced.

Recruitment and Informed Consent

Subjects will be identified from medical record review and recruited in person at the Smilow Cancer Hospital Thoracic Oncology clinic. Study staff will inform the treating clinician of potential participation in the study. If the treating clinician agrees to participation in the study, patients will be approached while they are waiting for their standard of care visit or immediately after the visit. Study staff will explain that participation is voluntary and that the participant may choose to end their study participation at any time. A study handout will be provided if the patient is interested. After 2 days, study staff will contact the patient by phone to inquire about participation. If interested, a visit to consent the patient and collect blood samples will be arranged. Documents provided to the patient during enrollment will include an informational handout, an educational pamphlet, HIPAA authorization, and the consent form. Patients will be instructed that refusal to participate will in no way affect their medical care.

If the patient agrees to participate, meets inclusion criteria, and signs the consent and HIPAA documents, study staff will explain the study's purpose, potential risks/benefits, and components of the study. If the patient volunteers to participate, the written consent and HIPAA documents will be reviewed and signed. Written consent forms will be collected and stored in a locked cabinet in a locked office in the Anlyan Center at Yale University.

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Demographics

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We anticipate that certain populations will be more or less likely to participate in physical activity regimens. However, other studies have shown that predictors for exercise are incompletely understood.[18] We will collect from medical records age, general demographics (e.g., race, height, weight, marital status, etc), cancer histology, disease stage, lung cancer treatment history, medical comorbidities (i.e., COPD, depression, and anxiety), treatment of medical comorbidities, smoking status, and performance status. This information may help in predicting who is more likely to participate in/benefit from increasing physical activity.

Surveys

Once consenting to participation, subjects will complete 4 voluntary, self-administered, validated surveys the same day after signing consent and at the end of their 12 week study duration : (1) Patient Health Questionnaire (PHQ-9), (2) Quality of Life Questionnaire (QLQ-C30, Version 3), (3) Modified Medical Research Council (MMRC) Dyspnea Scale, (4) the Physical Activity Questionnaire (PAQ). Study staff will explain the purpose of each survey, and subjects will complete the surveys in a private exam room. Study staff will be available to assist in survey completion, if needed.

Randomization will be performed via an envelope system. Prior to beginning the study, 40 envelopes indicating Intervention or Usual care group will be created and sealed using the randomization schema described above. After consenting to the study, the envelope corresponding to the patient's enrollment number will be opened.

At the end of the intervention, the PHQ-9, QLQ-C30, MMRC, and PAQ will be re-administered. In addition, a 10-item Feedback Survey in order to guide future studies. Participants may fill out the follow-up surveys at their regularly-scheduled appointments, via questionnaires mailed to the patient with a self-addressed envelope to return, or by phone with research staff. Study staff will try to obtain the final questionnaires within 4 weeks of the last day of activity collection, and in-person questionnaire completion will be attempted before mail-in questionnaires or telephone completion. Whether in person or over the phone, study staff will help the subjects remove the study account from the FitBit application and offer to assist in setting up their personal account. Those subjects in the usual care group will be provided a FitBit Flex 2 at the end of the study, and study staff will offer to help set up the device.

A total of 55 patients will be enrolled between Yale University, and the Medical University of South Carolina (MUSC). Those who agree to participate will be given a unique patient Study ID which will be used to identify completed surveys. De-identified survey data will be entered into the REDCap™ study database.

This study will be performed at both MUSC and Yale University, and de-identified data from both institutions will be stored on REDCap servers maintained by each institution. At the end of the study, data will be pooled for analysis. Since dates of treatment will be collected for the study, a shared data use agreement between Yale University and MUSC is in place.

Biomarkers

Fasting blood (> 12 hours) will be collected at baseline and at 12 weeks. Two 10-ml red-top tubes will be collected for serum, one 10-ml lavender-top tube will be collected for EDTA plasma, and two 4.5-ml light blue- top tubes will be collected for citrate plasma (total volume 39 mL of blood at each visit). Technicians will centrifuge the EDTA samples at 2,000 rpm for 15 minutes at 4°C within 1 hour of collection. Plasma and buffy coat will be separated, and, along with the serum, will be transferred into cryovials and labeled with freezer-proof labels with participant ID #s and date. All specimens will be stored temporarily at -20°C after aliquotting prior to delivery to the YCCI freezer (within 2 hours), and then stored at -80 degrees C until analysis. Each subject's baseline and follow-up samples will be assayed in the same batch, and an equal number of intervention and control samples also will be included in each batch. Appropriate blinded quality control samples (low and high levels) will be used

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to monitor the reliability of each assay. Insulin will be measured in serum using an enzyme-linked immunosorbent

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assay (ELISA) kit (Millipore Sigma, Burlington, MA; EZHI-14K). The other testing will be measured in the serum using kits from Life Technologies Inc, Carlsbad, CA: Leptin (KAC2281), soluble PD-1 (BMS2214), soluble PD-L1 (BMW2212), and CRP (KHA0031).

Subjects will be invited to allow blood samples (specimens) to be stored for future use regarding biomarker testing associated with lung cancer. Genetic testing will not be performed in this study. The storage and future testing of the blood samples is described in the consent, and subjects will have the option to decline future use of the sample as well as being contacted for future studies. If the subject declines future use of the samples, the specimen will be destroyed after this study is completed. If the subject changes their mind, samples will not be destroyed but the code connecting your identifiers to the samples will be deleted so your samples will then be anonymous.

Educational Session

Study staff will provide a brief educational session guided by an informational pamphlet addressing physical activity in lung cancer. Study staff will also discuss use of the FitBit device, the smartphone application, and methods by which subjects will be contacted (i.e., text messaging, e-mail, or telephone). Any subject questions will be answered.

Activity Monitoring and messaging

We will provide the subject with a FitBit Flex®, and ask him/her to wear it every day for 12 weeks, and request that it is charged it every 3-4 days (or when the battery is low). We will download the FitBit® application to the subject's smartphone and set up a generic email account and sign-in to the FitBit

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application using that account. We will show the subject how to use the FitBit® and how to use the phone application. The subject will be given contact information for study personnel in case he/she has any questions or problems.

Step counts are recorded in and collected from the FitBit website. Since an e-mail address is required for a FitBit account, a unique Yale e-mail address will be created (i.e., xlungc.#@yale.edu). This e-mail address will be used to activate the FitBit account but will not include patient information.

Patients will be asked to wear the FitBit Flex device every day and night for 12 weeks excepting when the device needs to be charged and when the device may get wet (e.g., bathing or swimming).

The first 7 days of step count monitoring will be used to establish an average daily step count. After 7 days, participants will be instructed to increase their daily step count by 400 steps/day from their average daily step count and will maintain this daily goal for one week. For example, if a patient has an average baseline of 8000 steps per day for the first 7 days, their goal will be to increase their step count to 8400 steps/day for the next 7 days (2nd week). This cycle will be continued weekly for a total of 12 weeks. If the patient reaches an average of >10,000 steps/day, instructions will be to maintain their current activity level.

The subjects' progress and step count goals will be relayed via twice/daily via smartphone text messaging. The text message application is secure, password-protected, and HIPAA-compliant. Text messages have been developed and will be the same for each patient (excepting replacement messages that will be sent when step counts are not collected, see below). Messages will include the subject's name, their most recent step count, their current step count goal, a motivational statement, reminders to wear and charge the device, and gain-framed messages. Gain-framed messages emphasize the benefits of a certain behavior[19] and have been shown to increase activity in older men,[20] healthy women,[21] and overweight patients.[22] An example text for Mr. John Doe: "John, last week was great! Your average was 5000 steps. Today, we'd like you to walk 5400 steps. Good luck!"

Three separate messages may replace the regularly-scheduled message if step counts are declining or not collected:

- If step counts are declining, the following text message may be used once, "Mr. Doe, your step counts are lower. Daily walking will improve your energy level! Call us with problems."
- If a step count is not collected for 1 day, the following text message will be used once, "John, your step counts are low. Please wear and sync the FitBit. Walking improves fatigue. Call with questions."
- If a week is "unusable" per study definitions, the following text message will be used once, "John, we missed steps for 3 days last week; too few to average. Please wear the FitBit every day; try for (average+400)!

If no step counts are recorded for 2 or more days, the study team will call the patient to evaluate for difficulty with the FitBit device. If difficulty with the device is discovered, a member of the study team will arrange to meet the patient at a regularly-scheduled clinic visit.

Due to patient feedback during the initial part of the study, if a patient has "0" steps recorded, the line referencing how many steps were taken will be deleted from the text message. Specifically, we will not send text messages saying, "John, you walked 0 steps today."

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At the end of the 12-week period, usual care participants will be provided a FitBit device. Study staff will offer to help remove the study account from intervention group participants and assist in setting up personal accounts in both the intervention and usual care groups. De-identified activity data from will be added to the REDCap™ study database. Recorded step counts will be rounded to the nearest whole number.

Sleep Monitoring

Because recent studies have shown that poor sleep quality is common in patients with lung cancer,[23] and poor sleep quality is associated with lower QoL,[24] total sleep time and the number of awakenings will be collected. Collection of nightly sleep time and number of awakenings will not influence the specific aims of this study but may guide future studies. Sleep data will also be recorded in the REDCap™ study database. Recorded values will be rounded to the nearest whole number.

5. Genetic Testing N/A ☒
   a. Describe
   i. The types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome sequencing, genome wide association studies, or animal studies are planned
   ii. The plan for the collection of materials or the conditions under which material will be received
   iii. the types of information about the donor/individual contributors that will be entered into a database
   iv. the methods to uphold confidentiality
   b. What are the conditions or procedures for sharing of materials and/or distributing for future research projects
   c. Is widespread sharing of materials planned?
   d. When and under what conditions will materials be stripped of all identifiers?
   e. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is anonymized) or material destroyed)?
   f. Describe the provisions for protection of participant privacy

Describe the methods for the security of storage and sharing of materials

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

This study will recruit adult patients with any stage non-small cell lung cancer who are prior to treatment, receiving active treatment, or have completed active treatment. Patients must be willing to wear a wrist-bound accelerometer, have access to a smartphone, and willing to download the FitBit application to their smartphone. Patients with impairments in memory, communication, or ambulation will not be enrolled.

As the patient's treating clinician is in the best position to judge their appropriateness for low impact physical activity, the treating oncologist will be involved in the decision to include the patient in the study.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children ☐ Healthy ☐ Fetal material, placenta, or dead fetus

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☐ Non-English Speaking ☐ Prisoners ☐Economically disadvantaged persons

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☐ Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses
☐ Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?

Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

Inclusion criteria:

- Pathologic evidence of non-small cell stage lung cancer (NSCLC)
- Approval of the treating clinician
- Adult patients (age >21 years) willing to wear a FitBit® device (FitBit, Inc., San Francisco, CA)
- Access to a smartphone, agree to receive twice/daily text messages for 12 weeks (including any costs), and willingness to download the FitBit application to their smartphone.

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- Low activity level as judged by a brief physical activity questionnaire (i.e., <150 minutes/week of moderate - intensity exercise, <75 minutes/week of vigorous aerobic exercise, or an equivalentcombination).

Exclusion criteria:
- Memory impairment (as judged by the treating clinician)
- Communication impairment (as judged by the treating clinician)
- Treating clinician's request not to alter physical activity
- Physical inability to safely walk (as judged by the treating clinician)

9. How will **eligibility** be determined, and by whom? Write here

Eligibility (i.e., meeting inclusion criteria and not having exclusion criteria) will be determined by the study staff during medical record review. The treating oncologist will confirm the patient's appropriateness for the study. If inclusion criteria are met (and no exclusion criteria are identified), then the physical activity questionnaire will be used to confirm eligibility.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Potential Risks

There are no major associated risks or harms with the collected surveys. Survey content may be minimally associated with psychological discomfort if the participant interprets the question as invasive.

In multiple published studies and reviews, low-impact physical activity interventions are considered safe in patients with lung cancer.[3] In a recent review of patients with advanced cancer (multiple cancer types), 6 minor musculoskeletal adverse events were reported.[25] Estimated patient risk with the proposed intervention is, therefore, low. Since this study prioritizes implementing standard-of-care techniques, we have not pursued safety monitoring. Put another way, since walking is not restricted in patients outside the research arena, no increased risk is suspected.

Drawing blood has a minor risk of bleeding, bruising, infection, phlebitis, inflammation, discomfort, or blood clot at the site of the injection. Pressure will be applied to where the blood was drawn afterwards to stop the bleeding. The subject may also feel dizzy or faint during or after the blood draw. We will suggest that they lie down and will provide them with fluid and snacks.

Loss of confidentiality is also a risk in this study. Techniques to protect data will include (1) storage of consents/questionnaires in a locked office and locked cabinet, (2) storage of labeled blood samples in a YNHH facility, (3) storage of electronic data within a protected network, and (4) use of a password-protected database with de-identified data.

11. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Risk of psychological discomfort

The subjects will be informed that if (s)he agrees to participate (s)he may choose to end the survey at any time, thereby minimizing any minimal psychological discomfort that may be experienced. The subjects will be reassured that their refusal to participate will in no way affect their medical care. If a subject indicated (s)he had feelings of being "better off dead" in the PHQ-9, he/she will be assessed by a member of the research team to be sure the subject understood the question and answered it accurately. If the subject is actually suicidal,

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they will be referred for urgent psychiatry evaluation, per standard of care.

Risk of blood draw

We will apply pressure to the site of the injection to make sure that we stop the bleeding. There will also be gauze over the wound that will clot the site. If they are feeling dizzy or faint we will lay them down until they feel better. There will also be snacks and drinks at the HRU.

Risk to confidentiality

Consent and HIPAA forms will be stored in a locked cabinet in a locked office in the Anlyan Center at Yale University. Subjects will be assigned a unique subject ID. An electronic spreadsheet will be stored on the Yale network and keep track of screened patients, enrolled patients, their assigned subject ID, cell phone

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number, cell phone carriers, and dates of interaction with the study team. Questionnaire data will be collected on forms identifiable only by Study ID number to protect the subject's confidentiality. The completed paper copies of the surveys and consents will be stored in a locked cabinet in a locked office in the Anlyan Center at Yale University. De-identified survey and activity data will be entered into a secure REDCap™ database created for this study; the de-identified data will be exported at study's end for analysis.

Since this study will be performed at both MUSC and Yale University, de-identified data from both institutions will be stored on a REDCap server maintained by MUSC. A shared data use agreement between Yale University and MUSC is in place.

Screening for adverse events will be accomplished by asking subjects to contact the study team by phone or email if they fall, are admitted to the hospital, or develop a musculoskeletal injury. In addition, at the end of the study period the study team will ask patients about adverse events during the study and perform a chart review to evaluate for falls, hospitalizations, or musculoskeletal injuries.

If an adverse event is identified, study staff will gather data about the injury (i.e., date of injury, type of injury, if injury was related to walking) and document the information in the REDCap database. Study staff will also contact the treating Oncologist to ensure he/she is aware of the injury and is in agreement with ongoing activity escalation. If no activity escalation is recommended, future texts will not recommend increased walking distances until recommended by the clinician.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
        i. Minimal
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
        i. Not applicable
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk

    d. For multi-site studies for which the Yale PI serves as the lead investigator:
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

Screening for adverse events will be accomplished by asking subjects to contact the study team by phone or email if they fall, are admitted to the hospital, develop a musculoskeletal injury, or have concerns about their physical activity. In addition, the study team will perform a chart review at the end of 12 weeks to evaluate for falls, hospitalizations, or musculoskeletal injuries. If an adverse event is identified, details will be collected and documented by the study team via the Adverse Event Documentation form. Study staff will gather data about the injury or event (i.e., date of injury, type of injury, if injury was related to walking). study staff will contact the treating Oncologist to ensure he/she is aware of the event and is in agreement with ongoing activity escalation. If no activity escalation is recommended, future texts will not recommend increased walking distances until recommended by the clinician. The treating Oncologist and site PI will determine if the adverse

event was related, possibly related, or unrelated to the study. All serious adverse events (SAE; e.g., death, shortness of breath, chest pain, falls, or hospitalizations) will be reported to the Institutional Review Board in addition to being discussed with the treating oncologist. Outside participating institutions will immediately report SAEs to the Yale Lead Investigator. Adverse events that are unexpected, related or possibly related, but not serious will also be reported to the IRB to ensure the process is safe.

ii. What provisions are in place for management of interim results?

An interim analysis evaluating study acceptability to patients and comparing patient participation to our prior work (using weekly phone calls) has been performed. No further analysis is planned until the study is completed.

iii. What will the multi-site process be for protocol modifications?

If protocol modifications are necessary, both Yale University and MUSC investigators will agree to the protocol modifications, and IRB approvals will be obtained at both sites.

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data Analysis

This portion of the study is to focus on feasibility of increasing physical activity via an exercise regimen and adherence with study recommendations. As a feasibility study, we will aim to enroll n=55 subjects. Simple descriptive statistics (e.g. percentages, confidence intervals, means, medians, etc.) will be utilized where necessary and calculated using SAS v9.3. Exploratory analyses will involve measuring associations (i.e. Spearman rank correlations) between activity measurements and changes in survey domain scores.

Primary study endpoints will include the following: (1) overall number and percentage of patients increasing their average daily step counts over 84 days and (2) adherence with study recommendations. Adherence will be defined as (the number of weeks a patient achieved the recommended walking goal)/(the number of recommendations made). Other endpoints will include biomarkers in blood (C-reactive protein, leptin, insulin, PD-1, and PD-L1), survey-specific domain scores (e.g. QLQ-C30 physical functioning, bodily pain, etc.), changes in those domain scores after the 84-day period, and analysis of feedback questionnaires (using simple statistics).

Within this phase, statistical analyses will involve the use of Spearman correlations to assess the extent to which changes in step counts over time are associated with changes in health related QoL domain scores. Since step counts will be measured daily, we will also construct generalized linear mixed models (GLMMs) to assess these relationships. The GLMMs will allow us to account for the fact that step counts will likely be correlated within individuals over time. If sleep time and number of awakenings can be collected, Spearman correlations will also be calculated for step counts and survey-specific domain scores.

Sample size justification

We will calculate the proportion of patients who are willing to wear and utilize the Fitbit® Flex™ pedometer. Based on prior studies in healthy patients, we anticipate that consent to participation and compliance with the device can reach 70-80%.[26] Our adherence will surely be lower due to enrolling patients with lung cancer. With n=50 subjects participating in activity monitoring and survey collection, estimates of adherence and survey domain scores will be sufficiently precise. For example, should 40 of the 50 subjects be fully compliant, the 95% confidence interval for that compliance rate will range from 66% to 90%, providing

evidence that this intervention is feasible in this patient population. Confidence intervals on mean estimates of

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the survey domains would span approximately ±0.3 standard deviation units. With n=50 subjects included in the follow-up assessments of association, we will also be able to detect correlations as small as r=0.4 with 80% power, assuming 2-sided hypothesis testing and an alpha level of 0.05.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

4. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

Not applicable.

5. Continuation of Drug Therapy After Study Closure ☒Not applicable to this project

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol:
      A) 40 subjects
   b. If this is a multi-site study, give the total number of subjects targeted across all sites:
      A) 40 subjects

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trialregistries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media(Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

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a. Describe how potential subjects will be identified.

Subjects will be identified by medical record review at the scheduled appointment in the Thoracic Oncology Clinic at Smilow Cancer Hospital. To confirm appropriateness, the treating Oncologist will be informed prior to study inclusion.

b. Describe how potential subjects are contacted.

Subjects will be approached at their standard of care Oncology clinic visit. There will also be a follow-up phone call after approaching them at the clinic visit to determine their interest in the study.

c. Who is recruiting potential subjects?

Subjects will be recruited via the primary investigator or study staff.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship.

There are no clinical current relationships. Since Dr. Bade works in the Thoracic Oncology clinic, it is possible that would see enrolled subjects or those eligible for enrollment in his clinic. If Dr. Bade sees patients in both a clinical and research capacity, the roles will be clearly distinguished during the clinic visit.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website athipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

HIPAA authorization will be obtained during enrollment in the study. Authorization for medical record review to determine if the subjects meets inclusion criteria is not practicable since many patients will not meet enrollment criteria.

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

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The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Subjects will be recruited in person at the Smilow Cancer Hospital Thoracic Oncology clinic. Study investigators and study staff will inform the treating clinician of potential participation in the study, and patients will be approached while they are waiting for their standard of care visit or immediately after the visit. Study staff will explain the following: goals of the study, groups in the study (i.e., intervention group and usual care group), length of the study, anticipated risk/benefits of study involvement, measures taken to minimize risk, and requirements for participating in the study (i.e., need for a smartphone, willingness to download a FitBit application to the smartphone, willingness to wear an accelerometer for 12 weeks, and willingness to receive 2 text messages/day for 12 weeks). The patient will be given the opportunity to ask questions. Study staff will also explain that participation is voluntary, and any participant may choose to stop participating in the study at any time. Study staff will also explain that participation (or non-participation) in the study will not influence their clinical care. Documents provided to the patient will include an informational handout, an educational pamphlet, HIPAA authorization, and the consent form. If patients volunteer to participate, copies of the study consent and HIPAA form will be provided.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

A subject's appropriateness for study participation and capacity to provide informed consent will be assessed in 2 ways. First, study staff will screen patients via medical record review for exclusions. Patients with impairments in cognition or memory will not be included. Second, the treating oncologist will be approached to confirm the patient's appropriateness for the study. If the study staff member who is recruiting the patient is concerned about patient appropriateness for the study or understanding of the study/consent process, study staff will notify to the treating oncologist and Primary Investigator to discuss their concerns. Ultimately, the primary investigator and treating oncologist must agree to the patient's inclusion in the study. If either the oncologist or Primary Investigator have concerns regarding the patient's capacity or appropriateness for the study, the patient will *not* be enrolled.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Since communication between the study team and the patient is crucial and translated materials are not currently available, non-English speaking patients will not be enrolled in this study.

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As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ ☒Not Requesting any consent waivers

☐ Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☒☐ Requesting a waiver of consent:

☒☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

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For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?

  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

  ☒☐ No

- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒☐

  Why would the research be impracticable to conduct without the waiver? Consent waiver for medical record review to determine if the subjects meets inclusion criteria since many patients will not meet enrollment criteria.

- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *na*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

The four sources of data for this study are:

1) The medical record to determine demographic data, cancer histology and stage, cancer treatment history, medical comorbidities, drug treatment for medical comorbidities.
2) Survey instruments (as described above)
3) Biomarkers analyzed in blood (C-reactive protein, leptin, insulin, PD-1, and PD-L1)
4) Step count and sleep data downloaded from the Fitbit® device

The study database will contain date of birth, date of enrollment, demographic information, cancer treatment details, past medical history, and medication regimen (including psychoactive medication use). In the database, subjects will be identified by Subject Number. An electronic document linking the enrolled patient name and medical record number to the subject number will be maintained at each institution's office.

2. How will the research data be collected, recorded and stored?

Data from the medical record will be collected and directly stored in the REDCap database. Survey instruments will be collected on paper forms (identifiable only by Study ID) during the clinic visit and recorded in the REDCap database for future analysis. The paper copies will be stored in a locked office in the Anlyan Center. All activity and sleep data will be acquired from the FitBit website and stored directly in the REDCap database. Blood will be stored in the YCCI freezer on 300 George Street in New Haven.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable

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study data and the storage media indicated above during and after the subject's participation in the study?

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As above, data from the medical record will be collected and directly stored in the REDCap database. Survey instruments will be collected on paper forms (identifiable only by Study ID) during the clinic visit and recorded in the REDCap database for future analysis. The paper copies will be stored in a locked office in the Anlyan Center. All activity and sleep data will be acquired from the FitBit website and stored directly in the REDCap database. Lists of screened and enrolled subjects will be kept in password-protected Excel files that are stored on a limited access Yale drive (\\med1.med.yale.edu\home\721774c\Bade, Brett).

All paper documents will be maintained in a locked cabinet in a locked office in the Anlyan center. All documents excepting the consent and HIPAA forms will be identified by the patient's Study ID number. Similarly, subjects will be identified in the REDCap database by their subject number rather than their name or medical record. The text messages will identify the patients by first only, and no information about the patient's diagnosis, status, or treatment will be sent via the text messages. Text messages will reference the benefits of physical activity in chronic lung disease and lung cancer. At the end of the study, limited access databases at Yale and MUSC will be combined for data analysis. Since cancer treatment dates will be included, a data use agreement is in place between the institutions. No direct patient identifiers will be shared between Yale and MUSC.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

When the study is completed, patient documents will be maintained for 3 years in a locked office. After 3 years, documents from the study may be shredded on university campus by the site primary investigator. The shredded documents will be disposed of by the university team. Information on the de-identified database will be maintained in anticipation of future studies.

6. If appropriate, has a Certificate of Confidentiality been obtained? *Write here*

SECTION V: POTENTIAL

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Potential benefits for the individual include potential improvements in QoL, increased physical activity, better mood, and improved symptom control. These benefits are potential and should *not* be a reason for patient participation. Participants in both the intervention and usual care groups will receive FitBit Flex 2 devices at the end of the study.

The potential benefit to society is the ability for a low-impact activity regimen to reduce inactivity in patients.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?

Subject alternatives include not participating in the research study or asking their clinician about feasible and safe methods to increase physical activity levels at home (outside study participation).

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving thiscompensation.

No payments will be provided to subjects. Participants in both the intervention and usual care groups will receive FitBit Flex 2 devices at the end of the study.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

The FitBit devices will be provided at no cost, and the participant will be able to keep the FitBit upon completion of the study. The FitBit smartphone application is free.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? ***Write here***
   b. Where and from whom may treatment be obtained? ***Write here***
   c. Are there any limits to the treatment being provided? ***Write here***
   d. Who will pay for this treatment? ***Write here***
   e. How will the medical treatment be accessed by subjects? *Write here*

If the subject is injured while on study, he/she should seek treatment and contact the study doctor as soon as possible.

Yale School of Medicine does not provide funds for the treatment of research-related injury. If the subject is injured as a result of participation in this study, treatment will be provided. The subject or the subject's insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

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IMPORTANT

Will this study have a billable service? Yes ☒ No☐

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?

Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

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Figure 1: Average Daily Step Count vs Physical Functioning

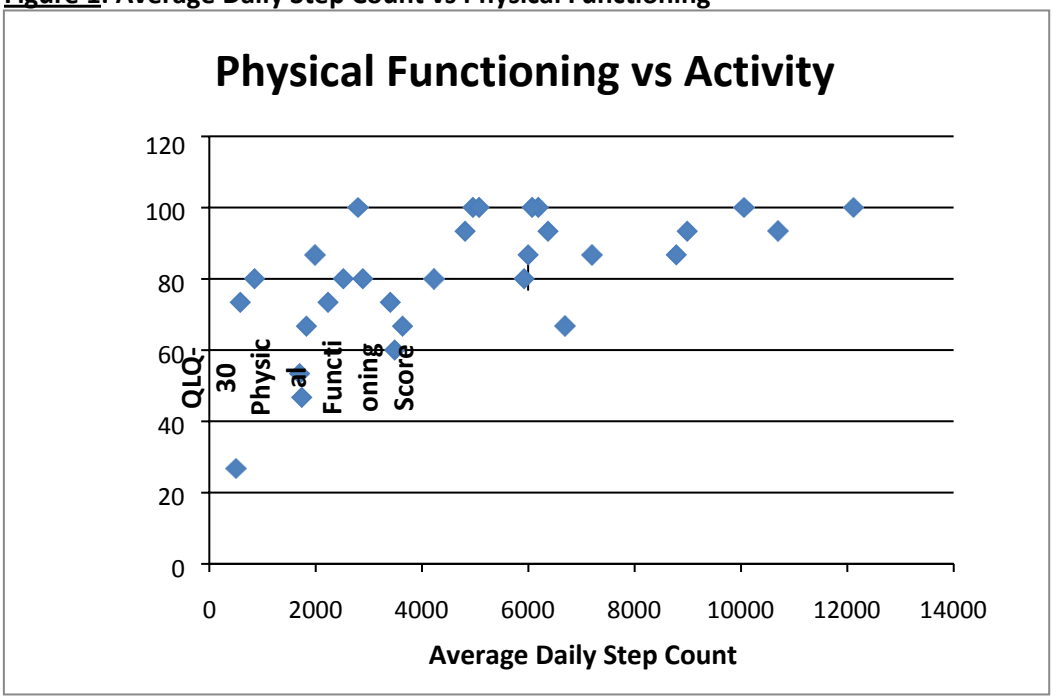

Figure 2: **Average Daily Step Count vs Dyspnea score**

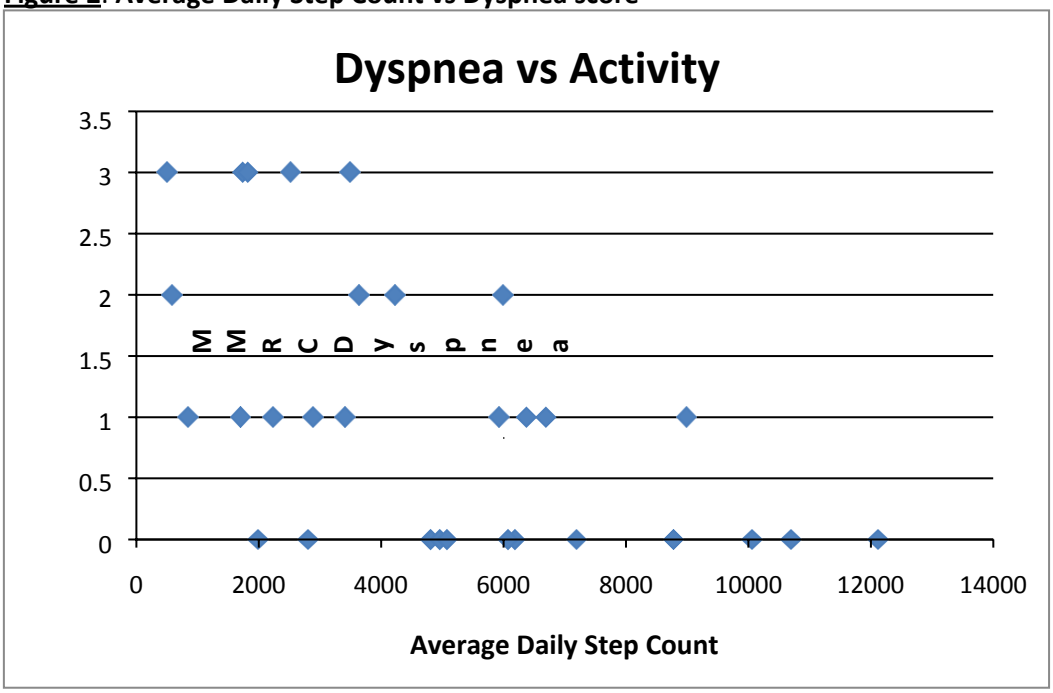

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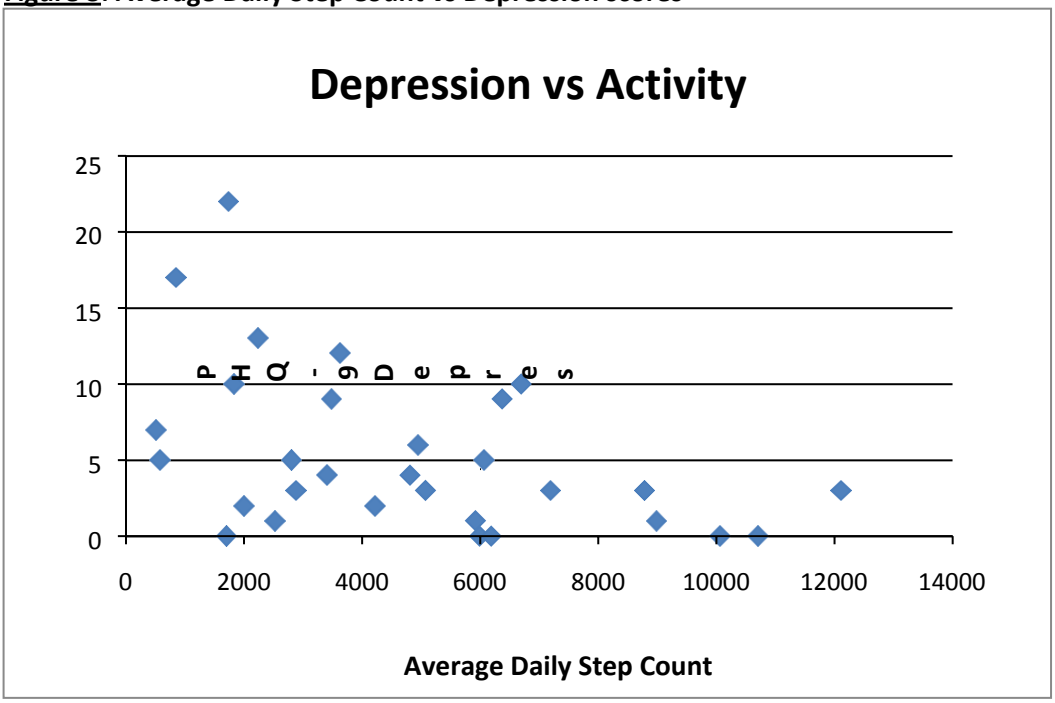
Figure 3: Average Daily Step Count vs Depression scores



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